BURDEN, ETIOLOGY, AND CONTROL OF HOSPITAL ACQUIRED INFECTION IN INTENSIVE CARE UNITS IN VIETNAM

By

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Abstract

Hospital acquired infection (HAI) is one of the most frequent adverse event in healthcare worldwide, affecting hundreds of millions of patients annually. In both developed and developing countries, this burden falls mainly on the critically ill. In Vietnam, HAI data are limited, particularly from the intensive care units (ICUs). Robust data are needed to evaluate these problems. This thesis addresses this need.

A point prevalence survey (PPS) of HAI and antibiotics use was conducted monthly at 15 ICUs of 14 tertiary and provincial hospitals across Vietnam from October 2012 to September 2013. Subsequently an observational study focused on ventilator associated pneumonia (VAP) and ventilator associated respiratory infections (VARI) at the ICUs of three referral hospitals in Hanoi and Ho Chi Minh City from November 2013 to November 2015.

Analysis of 3287 patients in the PPS showed that 29.5% patients had at least one HAI on the surveyed day of which 80% was hospital acquired pneumonia. Antibiotics were being administered to 84.8% patients. *A. baumannii*, *P. aeruginosa*, and *K. pneumoniae* accounted for > 50% of HAI pathogens with carbapenem resistance rates of 89.2%, 55.7%, and 14.9% respectively. The presence of an invasive device was associated with significantly higher risk for HAI.

The incidence of VAP and VARI in 374 patients analysed as part of the second study was 9.9% and 24.6% respectively with corresponding incidence densities of 7.6 and 21.4 episodes/1000 ventilation days respectively. Patients with VARI had an excess ICU stay of 11 days, ventilation duration 12.5 days, antibiotic consumption 11 DOT; and ICU cost 2189 US$ compared with those without VARI. Given an estimated 22,570 patients admitted to the ICUs of 14 surveyed hospitals in 2012 and VARI prevalence of 24.6%, we would expect 5552 patients developed VARI leading to an extra 69,403 ventilation days, 61,074 ICU days, 61,074 DOT antibiotic consumption, and an extra ICU cost of 12,153,810 US$. With a total

of 40 tertiary and 304 provincial acute care hospitals across Vietnam, the extra cost for VARI nationally would be many times higher.

In conclusion, this thesis provides compelling evidence that the burden of HAI in Vietnamese ICUs, particularly VAP/VARI, is substantial. There is also a high level of antibiotic consumption and widespread bacterial resistance to carbapenem antibiotics. Effective infection control measures and antibiotic stewardship programmes are urgently needed to address these problems in Vietnamese ICUs.

Co-Authorship

The majority of the work presented in this thesis was carried out by me with essential support from my supervisors and colleagues. I implemented most of the work with guidance from the study directors, Professor Heiman FL Wertheim, Professor Hakan Hanberger, and Dr. Behzad Nadjm.

The point prevalence survey was done in collaboration with 14 hospitals under the management of the National Hospital for Tropical Diseases and Oxford University Clinical Unit in Hanoi. The ventilator associated pneumonia study was conducted with the support from Oxford University Clinical Unit in Hanoi and Ho Chi Minh City in cooperation with three hospitals: The National Hospital for Tropical Diseases, Bach Mai Hospital, and the Hospital for Tropical Diseases in Ho Chi Minh City. For the statistical analysis, I worked mainly myself with support from Mr. Vu Tien Viet Dung, statistician of Oxford University Clinical Unit (OUCRU) – Hanoi, Vietnam.

Throughout my PhD programme, I received great training from OUCRU faculties, my supervisors, and my third-party monitor.

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Finally, I would like to dedicate this thesis to my family, particularly my wife and children who have sacrificed to support and encourage me to accomplish this thesis.

Declaration

Except for the assistance presented in the authorship and acknowledgment, I can confirm that the majority of work presented in this thesis is my own and was conducted under the supervision of Professor Heiman FL Wertheim and Dr. Behzad Nadjm at Oxford University Clinical Research Unit in Hanoi, Vietnam. The work presented in Chapter 3 and 4 has been published in the PLOS ONE journal in 2016, which has been updated with more recent literature. This thesis has not been submitted for a degree or other qualification to any other universities.

Abbreviations

&	And
°C	The degree Celsius
AB	Antibiotics
ACCP	American College of Chest Physicians
AIDS	Acquired Immunodeficiency Syndrome
AMR	Antimicrobial Resistance
APACHE II	Acute Physiology and Chronic Health Evaluation Score
BAL	Bronchoalveolar Lavage
BMH	Bach Mai Hospital
BSI	Blood Stream Infection
BYT	Vietnam Ministry of Health
C3-R	3rd cephalosporin generation resistant
C3-S	3rd cephalosporin generation susceptible
CABSI	Catheter Associated Blood Stream Infection
CAI	Community Acquired Infection
Car-R	Carbapenems resistant
Car-S	Carbapenems susceptible
CDC	Centers for Disease Control and Prevention
CFU	Colony Forming Unit
CI	Confidence Interval
CLSI	The Clinical and Laboratory Standards Institute guidelines on Performance Standards for Antimicrobial Susceptibility Testing
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease

CPIS	Clinical Pulmonary Infection Score
CRBSI	Catheter Related Blood Stream Infection
CRUTI	Catheter Related Blood Urinary Tract Infection
DDD	Defined Daily Dose
DOT	Day of Therapy
ECDC	The European Centre for Disease Prevention and Control
ECMO	Extracorporeal Membrane Oxygenation
FiO_2	Fraction of Inspired Oxygen
Glyco-R	Glycopeptides resistant
Glyco-S	Glycopeptides susceptible
GDP	Gross Domestic Product
HAI	Hospital Acquired Infection
HAP	Hospital Acquired Pneumonia
HBV	Hepatitis B Virus
HCAI	Healthcare Associated Infection
HCV	Hepatitis C Virus
HELICS	Hospital in Europe Link for Infection Control through Surveillance
HIV	Human Immunodeficiency Virus
HTD	Ho Chi Minh City Hospital for Tropical Diseases
ICU	Intensive Care Unit
INICC	The International Nosocomial Infection Control Consortium
IPC	Infection Prevention and Control
IQR	Interquartile Ranges
IVAC	Infection related Ventilator Associated Complication
LMIC	Low and Middle Income Country
LRTI	Low Respiratory Tract Infection

MIC	Minimum Inhibitor Concentration
MIU	Million International Units
mm^3	Cubic Millimeter
MRSA	Methicillin resistant *Staphylococcus aureus*
MSSA	Methicillin susceptible *Staphylococcus aureus*
NA	Not applicable
NHSN	The National Healthcare Safety Network
NHTD	National Hospital for Tropical Diseases
OR	Odds Ratio
Oxa-R	Oxacillin Resistant
Oxa-S	Oxacillin Susceptible
PaO2	Partial pressure of arterial dissolved oxygen
PD	Patient Day
PEEP	Positive End-Expiratory Pressure
PN	Pneumonia
PNU1	Clinical Defined Pneumonia
PPS	Point Prevalence Survey
SOFA	The Sequential Organ Failure Assessment Score
SPSS	Statistical Package for the Social Sciences
SSI	Surgical Site Infection
UK	The United Kingdom of Great Britain & Northern Ireland
UK NEQAS	The United Kingdom National External Quality Assessment Service
UNK	Unknown or missing data
US	The United States of America
USA	The United States of America
UTI	Urinary Tract Infection

VAC	Ventilator Associated Condition
VAE	Ventilator Associated Event
VAP	Ventilator Associated Pneumonia
VARI	Ventilator Associated Respiratory Infection
VAT	Ventilator Associated Tracheobronchitis
VD	Ventilation Day
VRE	Vancomycin Resistant enterococci
WBC	White Blood Cell
WHO	World Health Organization

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Chapter 1

General introduction on hospital acquired infections

Hospital acquired infection is one of the most frequent adverse event in healthcare worldwide. In Europe over 4 million patients are estimated to be affected by hospital acquired infection every year, with an estimated prevalence of 7.1%. In the United States of America (USA) figures are similar with a 4.5% prevalence rate affecting an estimated 1.7 million patients annually. Data from developing countries is sparse with only 23 out of 147 countries reporting national-level data. However in these countries prevalence rates are generally higher, ranging from 5.7 – 19.1% [1].

Based on these figures, the World Health Organization (WHO) estimates hundreds of millions of patients are affected annually by a healthcare associated infection. In both developed and developing countries, the critically ill are disproportionately affected. Infection rates are significantly higher in developing countries, with levels at least twice those in the USA [1].

1.1. Definitions of terms

Nosocomial infections, healthcare associated infections (HCAI) and hospital-acquired infections (HAI) generally have similar, overlapping meanings. WHO defines healthcare associated infection as 'an infection occurring in a patient during the process of care in a healthcare facility which was not present at the time of admission'. Whilst this is similar to the definition of hospital-acquired infection (see below) it importantly also includes patients in long-stay residential or nursing homes. Nosocomial infection may refer to either HCAI or HAI but has a less clear definition and this term will therefore not be used in this thesis.

According to the WHO, "Hospital-acquired infections are infections acquired during hospital care which are not present or incubating at admission" [2]. The time frame for diagnosis of

HAI is dependent on the incubation period of the disease. However, infections that manifest over 48 hours after admission are generally accepted to be HAI [2, 3]. Thus all HAIs are by definition HCAIs, whilst HAI represent a subset of HCAI.

The use of epidemiological terms of HAI disease burden can vary between different studies and different reports. Here we have used prevalence of HAI to refer to proportion of subjects affected during a point prevalence survey (i.e. at a single point in time), incidence is used to describe the proportion of patients who may be affected during their hospital stay and incidence density is a term used for the frequency of infection per person day at risk (or more commonly 1000 person days at risk). Where the HAI is related to a device (see section 1.2 below) this may be expressed as a rate per 1000 device days to emphasize that the subject is only at risk when the device is in place.

1.2 Epidemiology of hospital acquired infections

1.2.1. HAI in high income countries

In many high-income settings there are robust national surveillance systems in place for reporting of HAI. These usually include reports of both the site and nature of infection and also the case-mix of patients. These systems employ a variety of surveillance techniques including mandatory reporting of certain HAIs (e.g. *Clostridium difficile* colitis, surgical site infections and *Staphylococcus aureus* bacteriemia in the United Kingdom (UK) and intermittent point prevalence surveys.

HAIs are classified according to the major site of infection, for example urinary tract infection, blood stream infection, surgical site infection or pneumonia. The most common HAIs are lower respiratory tract infections (including pneumonia), surgical site infections, urinary tract infections, and blood stream infections. HAIs can be further classified depending on whether they relate to a device, which is specific for the infection site; endotracheal tube or tracheostomy tube and mechanical ventilation for pneumonia (generating the HAI designated

ventilator associated pneumonia or VAP), central venous catheter for blood stream infection (generating catheter related/associated blood stream infection or CRBSI/CABSI), urinary catheter for urinary tract infection (catheter associated UTI or CAUTI).

The European Centre for Disease Prevention and Control (ECDC) reported that the prevalence of HAIs in European industrialized countries ranged from 3.5% to 10.5%, with a mean of 7.1% based upon data collected during period 1996 to 2007 [4]. During 2011 – 2012, the ECDC conducted a point prevalence survey looking at HAIs in European acute care hospitals and reported HAI prevalence was 6.0% of all patients [5]. This ECDC report also showed that the HAI prevalence varied by hospital types, being highest in tertiary hospitals at 7.4%, then specialized hospitals at 6.0%, and dropping to 5.0% in both secondary and primary hospitals [5]. In the USA, there was an estimated incidence of HAI of 4.5% in 2002, corresponding to 9.3 infections per 1000 patient days and 1.7 million affected patients [6]. A point prevalence survey of 183 acute care hospitals in the USA conducted almost a decade later found remarkably consistent results, showing that 4.0% of over 11,000 patients surveyed had HAI [7].

ICU patients, neonates and those with transplants or burns are at greatest risk of HAI. ECDC surveillance in European hospitals in 2011 – 2012 found that 19.5% patients in ICUs had at least one HAI compared to a mean rate of 5.2% for all other specialties [5]. In the USA, more than 4000 health-care facilities regularly report data on ICU-acquired infections to the National Healthcare Safety Network (NHSN) established by US Centers for Disease Control and Prevention (CDC: http://www.cdc.gov/nhsn/). In one of the largest recent studies, Magill et al, looking at 183 acute care hospitals in the United States in 2011, showed that HAI prevalence in ICUs was 9.1%, as compared to 2.9% on general wards [7]. Looking specifically at device associated infections in the USA, Dudeck et al. demonstrated that variations occur depending on the type of ICU; for example, incidence density of central line related blood stream infection (episodes/1000 device-days) varied from 0.8 in surgical

cardiothoracic ICUs to 1.4 in trauma ICUs and 2.9 in burn ICUs whilst VAP incidence density ranged from zero in respiratory ICUs to 4.7 in trauma ICU and 4.9 in burn ICUs [8].

Hospital–wide European data from 2008 showed the most frequent HAIs were pneumonia (19.4% of all HAI), surgical site infections (SSI) (19.6%), urinary tract infection (UTI) (19%), bloodstream infections (BSI) (10.6)%, and gastro-intestinal infections (7.6%) [5]. Similarly the more recent point prevalence data from acute care hospitals confirmed UTI was the most frequent type of HAI, accounting for 36% of HAI, followed by SSI (20% of HAI), BSI and pneumonia (11% HAI) [6].

The most common HAIs in the European ICUs were respiratory infections (pneumonia and lower respiratory tract infections, accounting for > 40% of HAIs) and BSI (about 18% of HAIs) [5]. Similar data were reported in a comprehensive WHO review in 2011; the most common HAIs in adult ICUs across developed countries were VAP (32% of HAIs), followed by CAUTI (20%), and CRBSI (20%). The pooled incidence density/1000 device-days of VAP was 7.9 episodes, CAUTI was 4.1 episodes, and CRBSI were 3.5 episodes [1]. All these common HAIs in ICUs are associated with the use of invasive devices, emphasizing that the high use of invasive devices puts ICU patients at increased risk of HAI. The USA National Nosocomial Infections Surveillance system also highlighted this, showing that 83% of episodes of hospital-acquired pneumonia were associated with mechanical ventilation, 97% of UTIs occurred in catheterized patients, and 87% of primary BSI in patients with a central line [9].

1.2.2 HAI in low and middle-income countries

There is little information on HAIs from low and middle income countries (LMICs). In 2010, only 23 out of 147 developing countries (16%) reported a functioning national surveillance system and 97 of 147 (66%) developing countries had no published data at all [1].

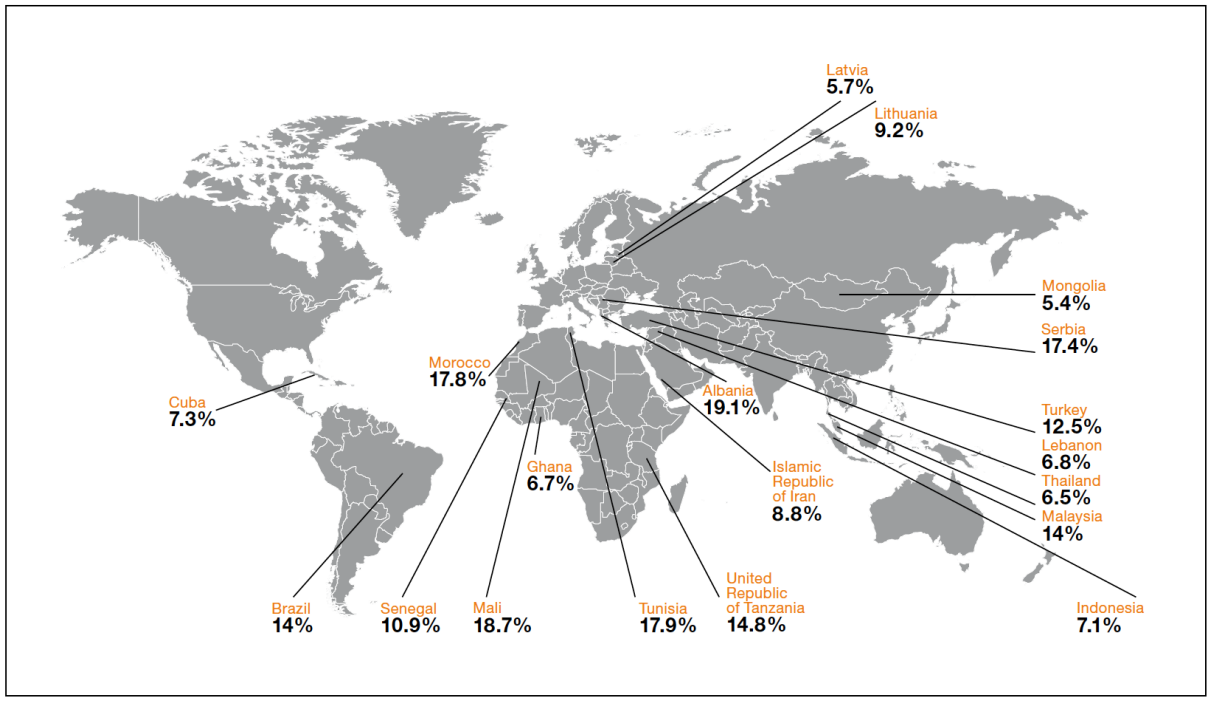


Figure 1 – 1: Prevalence of healthcare-associated infection in low- and middle-income countries, 1995-2010. Reproduced from [1]

Nevertheless, HAI appears to be at least as important a problem in resource-limited settings. WHO reports that in LMICs, the prevalence of HAI ranges from 5.7% to 19.1% (Figure 1 – 1), with an average of 10.1 HAIs per 100 patient admissions (95% CI 8.4 – 12.2) [1]. Whilst it has been observed that the prevalence of HAI in resource limited settings in high-quality studies is higher than in low-quality studies (15.5% vs 8.5%) [10], the WHO report noted that over half the studies were of low quality. Of note both low and high quality studies give estimates that are higher than those in developed countries. The most frequent types of HAI were: SSI (29.1% of all HAI), UTI (23.9%), BSI (19.1%), hospital acquired pneumonia (HAP; 14.8%), and other infections (13.1%) [10]. One of the few studies to gather longitudinal data was a study in Kenya that was limited to paediatric admissions and BSI found an incidence density of 1 per 1000 patient days [11].

In LMICs, similar to better resourced settings, HAI incidence is higher in ICU compared to other hospital settings. HAI incidence ranged widely between reports from 4.4% to 88.9%

with a pooled incidence of 35.2% and pooled incidence density of HAI was 42.7 episodes per 1000 patient-days [1].

1.2.3 Surveillance and diagnosis of VAP and VARI

For accurate surveillance of HAI good and robust definitions are required. These may be different to those used in routine clinical care and diagnosis. For many HAIs definitions are relatively straight-forward and can be defined using guidelines such as those provided by CDC from 1988 or later updates by CDC and the European Centre for Disease Control (ECDC) [12-14]. These definitions will usually include clinical criteria such as fever combined with positive microbiological findings. However definitions vary and when interpreting published literature it is important to take into account the exact definitions used.

1.2.3.1 Ventilator associated respiratory infections (VARI) - definitions and diagnosis

One particularly problematical area is the diagnosis of ventilator-associated respiratory infections, comprising ventilator associated pneumonia (VAP) and ventilator associated tracheobronchitis (VAT), which causes much debate and controversy [15]. This is in part due to the lack of consensus over what actually constitutes VAP clinically combined with the lack of a gold standard diagnosis. It should be noted that there is a clear distinction between the criteria used for VAP diagnosis by clinicians managing patients in the ICUs and by surveillance. There is also difference in definitions of VAP between different studies as guidelines for VAP diagnosis have changed over time. Surveillance of VAP has also been proposed as a marker of quality of service (implying that with the correct care and attention incidence can be reduced significantly) and in some situations there may be strong financial incentives not to report the condition further complicating data interpretation [15]. In response to the apparently low surveillance rates of VAP (sometimes 0%) reported in some centres in the US [8] which were at odds with clinical data, definitions were changed towards what was felt to be more objective ones. However criteria are still subjective and non-specific due to the

complexity of both the disease and the critically-ill patients affected. Thus there are no universally-accepted standard surveillance criteria for VAP [16].

Currently international consensus is that clinically, VAP should be suspected when the patient intubated for over 48 hours, has new and persistent infiltrates on the chest x-ray, with a deterioration in gas exchange, signs of infection (fever, leukocytosis, increased purulent sputum), and positive culture of a lower respiratory tract specimen [13, 17-19]. However, radiographic criteria are neither specific nor sensitive, and many other clinical syndromes common in ICU patients, such as congestive heart failure, atelectasis, pulmonary embolus and systemic sepsis can lead to deterioration in gas exchange and other so-called signs of VAP [13, 20, 21]. In an attempt to resolve this, improve the accuracy of VAP surveillance and permit electronic record based capture of cases modified criteria which assess more objective changes in the ventilation setting, like fraction of inspired oxygen (FiO_2) and positive end-expiratory pressure (PEEP), have been proposed [22]. Chest radiograph has also been removed from these criteria and a new classification of ventilator associated conditions (a subgroup of which is VAP) proposed in 2013 by CDC [23]. In 2016, further changes in the VAP definition, possible and probable VAP were removed and now only one type of possible VAP is possible based on three sign groups: oxygenation deterioration, clinical signs/symptom of infection and antibiotic use, and microbiology results [24]. X-ray criteria have not been in CDC surveillance definitions for VAP since 2013, yet remain important to many clinicians and academics seeking clear end points for studies. CDC and some common criteria for identifying VAP is presented in Table 1 – 1. Detailed criteria of CDC/NHSN 2013 and 2016 for recognizing VAP are presented in Figure 1 – 2 and Figure 1 – 3.

Table 1 - 1. Summary of published criteria for VAP diagnosis in common use

Criteria	CDC/NHSN 2013 - possible VAP [23]	CDC/NHSN 2008 – PNU1 [13]	CPIS (suspect VAP if score >6) [25]	HELICS [26]	ACCP [27]	Johanson's criteria [17]
Pulmonary clinical signs	Worsening oxygenation after ≥ 2 calendar days of stable or improving period: Minimum daily FIO_2 increase ≥ 0.20 remain 2 days OR minimum daily PEEP values increase ≥ 3 cm H_2O remain 2 days	At least two of: - New purulent sputum or change in character - New onset or worsening cough, dyspnea, or tachypnea - Auscultation suggestive worsening gas exchange (desaturation, PaO2/FiO2 ≤ 240, increasing FIO_2 or ventilation requirements)	PaO2/FiO2 ≤ 240 and no ARDS: 2	At least one of these (2 if qualitative aspirate culture or if culture is negative): - New purulent sputum or change in character - New onset or worsening cough, dyspnea, or tachypnea - Auscultation suggestive worsening gas exchange (desaturation, PaO2/FiO2 ≤ 240, increasing FIO_2 or ventilation requirements)		
Systemic response	At least one of: - Temperature >38°C or < 36°C - WBC >12.000/mm^3 or < 4.000/mm^3 AND - New antimicrobials use for > 4 days	At least one of: - Temperature >38°C or < 36°C - WBC >12.000/mm^3 or < 4.000/mm^3 - Altered mental status with no other cause for patient > 70 years old	- Temperature ≥38.5°C and ≤ 38.9°C: 1 - Temperature ≥39°C or ≤ 36.5°C: 2 - WBC >11.000/mm^3 or <4.000/mm^3: 1 - WBC >11.000/mm^3 or <4.000/mm^3 AND band form≥ 500: 2	At least one of: - Temperature >38°C or < 36°C - WBC >12.000/mm^3 or < 4.000/mm^3	At least two of: - Temperature >38°C or < 36°C - WBC >12.000/mm^3 or <4.000/mm^3 - Purulent secretions - Decreased PaO2	Fever and Leukocytosis
Chest x-ray		One of these on ≥ 2 series x-rays for patients with underlying diseases or ≥ 1 x-ray for patients without - New or progressive and persistent infiltrate - Consolidation - Cavitation	Diffuse infiltrate: 1 Localized infiltrate: 2	Image suggestive of pneumonia (two or more required for patients with underlying cardiac or pulmonary disease)	New alveolar infiltrates or an air bronchogram sign, or if the findings have worsened	New or progressive infiltrate
Respiratory specimen examination	- Purulent respiratory secretions defined as that contain >25 neutrophils and <10 squamous epithelial cells per low power field. - Positive culture (qualitative, semi-quantitative or quantitative) of sputum		- Secretions but not purulent: 1 points - Purulent respiratory secretions: 2 - Semiquantitative culture of tracheal aspirate >1+: 1 point - Semiquantitative culture of tracheal aspirate >1+ and same pathogenic seen on Gram stain > 1+: 2	Positive quantitative culture		Purulent respiratory secretions

CDC/NHSN = US Centers for Disease Control and Prevention/National Healthcare Safety Network; PNU1 = clinically defined pneumonia; ACCP = American College of Chest Physicians; CPIS = Clinical Pulmonary Infection Score; HELICS = Hospital in Europe Link for Infection Control through Surveillance; VAP = ventilator-associated pneumonia.

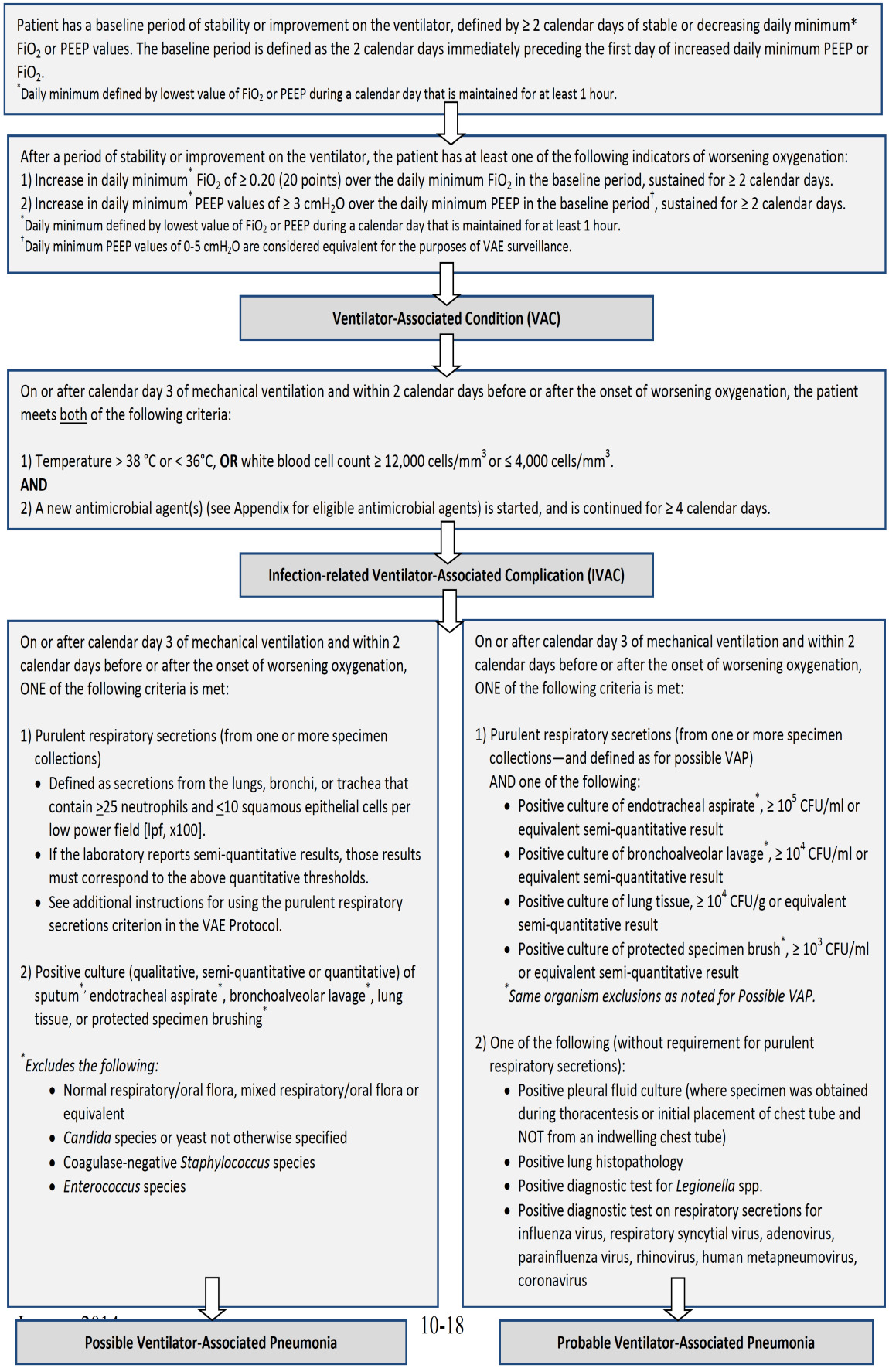


Figure 1 - 2. CDC criteria for ventilator associated events surveillance 2013.

Reproduced from [23]

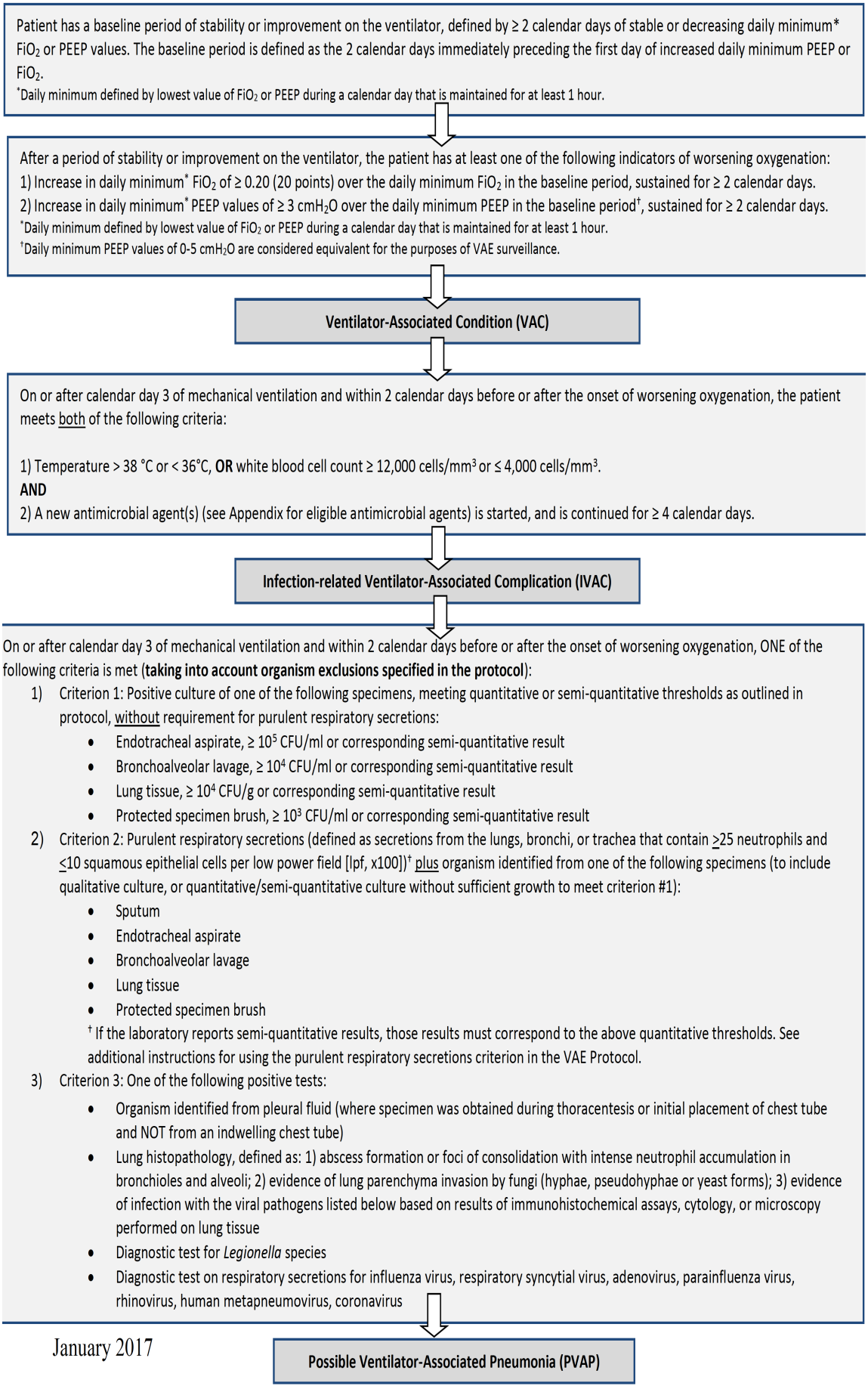


Figure 1 - 3. CDC criteria for ventilator associated events surveillance 2016.

Reproduced from [24]

There has been increasing awareness of ventilator-associated tracheobronchitis (VAT) as a syndrome, and attempts to distinguish ventilator-associated infection of the lower respiratory tract (VAT) from VAP. Like VAP, there are no standard criteria for VAT, and perhaps even less consensus as to its significance, with some authors seeing it as a milder form of infection and others as an early stage of VAP [28]. Most common used VAT definitions include fever > 38^{o}C or leucocytosis without other cause, purulent tracheal secretion, positive tracheal aspirate culture (≥ 10^{5} colony forming units (cfu)/ml), and the absence of new infiltrate on chest radiograph in patients ventilated for > 48 hours [29-33]. These VAT criteria overlap with clinical VAP definitions, fundamentally distinguished by the absence of radiographic changes [18]. However in practice, the differentiation between VAT and VAP is challenging and may represent timing of radiological examination or its interpretation. Removing the requirement for new and persistent infiltrate on chest x-ray from VAP criteria has been proposed [34] due to its subjective nature and difficulty excluding other non-infective causes of chest x-ray changes. Also the term ventilator associated respiratory infection (VARI) has been used to encompass both VAT and VAP [35].

The results of microbiological tests form one of the criteria for both VAP and VAT diagnosis, however microbiological results alone are not sufficient for a diagnosis of VAP or VAT. In intubated patients the lower airway is often no longer sterile and colonization with bacteria is common. Endotracheal aspirates may consequently show significant growth of bacteria commonly associated with VARI in the absence of systemic or even local signs of infection. Although bacteriological criteria are felt to be objective they may be dependent on the procedure used to take the specimen and confounded by the presence of colonizing organisms in intubated patients. Quantitative culture, to determine how heavy the bacteria growth is, and the presence of pus cells have been used as a way of differentiating true infection from colonization but there is no consensus regarding what density of bacteria growth differentiates the two [36, 37]. In general samples from deeper in the respiratory tree require lower numbers

of organisms to be considered significant. When combined with histological or clinical parameters, bronchoalveolar lavage (BAL, $>10^4$ cfu/ml), protected BAL ($>10^4$ cfu/ml), endotracheal aspirate ($>10^5$ cfu/ml) were associated with sensitivities of 22-50% and specificities of 45-100% in diagnosis of VAP using histological reference tests [20]. When histological and bacteriological tests were combined, sensitivities were 19-87% and 31-100% specificity [20]. Again the lack of gold standard diagnosis of VAP is a major problem when interpreting these results, developing diagnostic criteria and comparing different studies.

Despite these uncertainties, many studies used quantitative culture of endotracheal aspirate specimens with $\geq 10^5$ cfu/ml or semi-quantitative culture results showing moderate to heavy growth as meeting microbiological criteria for VAT or VAP definitions, as detailed in the review by Craven et al. [35]. However, although using higher cut-off's increases the likelihood of true pathogen isolation, it also lowers sensitivity and may lead to underdiagnosis of VARI in some cases. Conversely, lower cut-off values would increase sensitivity to detect pathogens and diagnose VARI, but have higher possible of false positive rates (ie isolates are not pathogens, just coloniser) [38]. Such an approach could lead to unnecessary antibiotic use and thereby increase antibiotic resistance.

1.2.3.2 Epidemiology of VAP and VARI

VAP is one of the most common HAIs in ICU. In the period from 2006 through 2008 in the United States pooled VAP incidence density was 2.97 episodes/1000 ventilation days, ranging from 0.5 to 10.7 episodes/1000 ventilation days [39]. ECDC surveillance in European ICUs in 2007 found that 7.0% of patients who stayed > 2 days in ICU developed pneumonia and incidence density of intubation-associated pneumonia ranged from 7.2 episodes/1000 intubation days to 22 episodes/1000 intubation days [40]. Lambert et al analysed the European database of ICU admissions between January 1st 2005 to December 31 2008, finding that 7.0% (8525/119699) of patients staying > 2 days in ICU developed hospital-acquired pneumonia, of which 90% (7675/8525) was VAP [41], giving a VAP incidence of

6.4% for patients staying in European ICUs for > 48 hours. Martin-Loeches et al found the incidence of VAP was 12% (8.8 episodes/1000 ventilation days) through a prospective international multicenter observational study on adult patients ventilated for > 48 hours at 114 ICUs in eight countries in Europe and South America between September 1st 2013 to July 31st 2014. In this study clinical, white blood cell, radiology, and quantitative culture criteria were used for the diagnosis of VAP and VAT [32]. Kollef et al. conducted a prospective observational study in 11 upper-middle and high income countries in four global regions over six months between March 2011 to March 2012, enrolling 1873 adult patients who were ventilated for between 48 hours and 7 days. They found that VAP incidence over the 30 days following enrolment was 15.6% globally, 13.5% in the United State, 13.8% in Latin America, and 16.0% in Asia Pacific in Europe (VAP being defined by local investigators) [42].

The epidemiology of VAT is less well studied, however there are some data. Nseir et al. conducted a prospective surveillance study for nosocomial tracheobronchitis (definition based on the Center for Disease Control criteria in 1988) in a 30 bed medical/surgical ICU in France from March 1993 to September 1999 on all patients ventilated for > 48 hours [29]. This study found that VAT incidence was 10.6% (201 among 1889 included patients) and that VAT was associated with an increase in mechanical ventilation time and ICU stay of about 14 days and 17 days respectively compared with those patients without VAT. In the study described above by Martin-Loeches et al. the VAT rate was 11% (10.2 episodes/1000 ventilation days) [32]. Agrafiotis et al. conducted a systematic review and meta-analysis including 17 studies on VAT published up to September 2008 found that rate of VAT was 11.5% [43]. Craven et al. also found that VAT incidence (diagnosed by two clinical signs and quantitative endotracheal aspirate culture) was 11% in patients ventilated for > 48 hours and 29% of these patients developed VAP later [30]. Karvouniaris et al. conducted a prospective observational study of 236 patients ventilated for > 48 hours between 2009 to 2011 in University Hospital Greece and found that VAT incidence was 18% (42/236) [44]. Dallas et al. conducted a prospective cohort study on intubated patients for > 48 hours at the surgical and medical ICUs of a tertiary

hospital in the USA over 1 year found that VAT incidence was just 1.4% while VAP incidence was 4.0% [31]. As a result, VAT incidence among ICU patients ventilated for > 48 hours ranged from 1.4% to 18% depended on surveyed sites.

1.2.3.3 VAP in resource-limited settings

In developing countries, VAP is also perceived to be a major problem. Rosenthal et al conducted a prospective multicenter surveillance study for device-associated HAI in 43 countries from Latin America, Asia, Africa, and Europe that were participating in the International Nosocomial Infection Control Consortium (INICC). The authors found that VAP incidence density (using the 2008 CDC definition) was 19.5 (18.7 – 20.3) episodes/1000 ventilation days in the period 2002-2007, decreasing to 14.7 (14.5 – 14.9) episodes/1000 ventilation days in period 2007 – 2012 [45]. Mathai and colleagues conducted a prospective study at a tertiary hospital ICU in India from December 1st 2010 to November 30th 2011 on patients ventilated for > 48 hours found that 38% (95/250) of enrolled patients developed VAP and the incidence density of VAP was 40.1 episodes/1000 ventilation days [46]. Song et al. reported VAP incidence of 25% vs 26.7% and incidence density of 29.7 and 27.4 episodes /1000 ventilation days in medical and surgical ICU respectively, at a 1500 bed university – tertiary hospital in China between January 2011 and June 2012 [47]. Arabi et al. conducted a systematic review on published papers on VAP from developing countries from January 1966 to April 2007 including 18 papers and reported the VAP incidence density ranged from 10 episodes in Thailand to 41.7 episodes/1000 ventilation days in Brazil [48]. Consequently, VAP incidence and incidence density ranged from 25% to 38% and 14.7 to 41.7 episodes/1000 ventilation days depended on settings.

1.3 Pathogenesis of hospital acquired infections

HAIs are caused by infectious agents originating from either endogenous or exogenous sources. Endogenous sources are the patient's own body sites, such as the skin, nose, mouth,

gastrointestinal tract etc. that are normally colonized by local microbial flora. These microorganisms can become invasive under certain favorable conditions and cause infection. Exogenous sources are those external to the patient, such as health care workers, visitors, medical devices, or the health care environment.

In hospitalized patients, the normal flora changes due to the use of antibiotics, and colonization by new bacteria present in the environment. Antibiotic use leads to a selective pressure on normal flora, i.e susceptible bacteria will be killed while bacteria resistant to the antibiotics used will survive, multiply and become predominant. In hospital, patients will also be in contact with the hospital environment and acquire local bacteria which are commonly antibiotic resistant as they are able to survive in the hospital environment where antibiotics are used commonly. Further the death of susceptible normal flora resulting from antibiotic use can open these sites to colonization by resistant flora from the environment. Finally the use of invasive devices, which use synthetic materials, allows bacteria that have adapted to survive on such artificial materials (for example the plastic of an endotracheal tube or central venous catheter) to reproduce and become dominant, whilst bacteria adapted to surviving on human tissue are disadvantaged and die off. These factors explain why the pathogens associated with hospital acquired infections are usually resistant to many antibiotics and are often different species to those encountered commonly in community acquired infections.

A report by WHO in 2011 on the global burden of HAI showed that the most frequent pathogens causing HAI were *Escherichia coli* (20.1%), *Staphylococcus aureus* (17.8%), *Pseudomonas* spp. (11.5%), Enterobacteriaceae (10.6%), *Candida* spp. (11.5%), Enterococci (6.5%), *Acinetobacter* spp. (5.8%), and coagulase-negative staphylococci (5.3%); and in ICUs they were *S. aureus* (21.8%), Enterobacteriaceae (20.2%), *Pseudomonas* spp. (17.2%), Enterococci (10.0%), *E. coli* (9.1%), *Candida* spp. (8.8%), coagulase-negative staphylococci (7.0%), and *Acinetobacter* spp. (5.1%). [1]

A point prevalence survey of HAI in European hospitals conducted by the European Center for Disease Control (ECDC) in 2011-2012 showed that the most common microorganisms reported for HAIs were broadly similar: *E. coli* (15.9%), *S. aureus* (12.3%), *Enterococcus* spp. (9.6%), *Pseudomonas aeruginosa* (8.9%), *Klebsiella* spp. (8.7%), Coagulase-negative staphylococci (7.5%), *Candida* spp. (6.1%), *Clostridium difficile* (5.4%), *Enterobacter* spp. (4.2%), *Proteus* spp. (3.8%), *Acinetobacter* spp. (3.6%). In this report, 41.2% of *S. aureus* was methicillin resistant (MRSA) [5]. Vancomycin resistance was reported in 10.2% of isolated enterococci and higher among *Enterococcus faecium* (19%) than *Enterococcus faecalis* (5.5%). Enterobacteriaceae non-susceptible to third generation cephalosporins and carbapenems were 33.4% and 7.6%, respectively. Non susceptibility to carbapenems was also reported in 31.8% of *P. aeruginosa* and 81.2% of *Acinetobacter baumannii* [5]. A report by ECDC on European hospitals for 2004 to 2006 showed that the most common pathogens of ICU-acquired pneumonia were *P. aeruginosa* 19.0%, then *S. aureus* 18.0% with MRSA representing 42.8% of these [4]. A study at a 15-bed surgical and neurosurgical ICU in Croatia, from September 2009 to March 2013 found that most common bacteria causing VAP were *Staphylococcus aureus* (21.1%), followed by *Pseudomonas aeruginosa* (19.0%) and *Acinetobacter* species (13.6%) [49]. Chi et al. reported that among 108 pathogens from 91 VAP patients in South Korea between January 2008 to December 2009, most common isolates were *S. aureus* 44%, *A. baumannii* 30%, *P. aeruginosa* 12%, and *Stenotrophomonas maltophilia* 7%, *K. pneumoniae* 6%, and *serratia marcescens* 2%; with 69% of *A. baumannii* isolates resistant to imipenem [50]. In a study on VAT from March 1993 to September 1999, Nseir et al. found that common pathogens of VAT in surgical and medical ICU (respectively) were *P. aeruginosa* (31.8% vs 28%), *S. aureus* (20.4% vs 17.8%), and *A. baumannii* (13.6% vs 26.5%) [29]. A review by Nseir et al. showed that the most common among 369 microorganisms isolated from 302 VAT episodes were *P. aeruginosa* 27% (101/369), *S. aureus* 20% (76/369) of which methicillin resistant *S. aureus* (MRSA) accounted for 69.7% (53/76), and *A. baumannii* 18% (67/369) [33].

In developing countries, the most common bacteria causing HAI are Gram-negative bacilli. A systematic review of 220 studies from 1995 to 2008 across 6 regions (Africa, the Americas, Europe, southeast Asia, eastern Mediterranean, and western Pacific) found that the most frequent pathogens identified for HAP (included VAP) was *Pseudomonas* spp. (29%) and *Acinetobacter* spp (24.0%) and for BSI was *S. aureus* (19%) and *Acinetobacter* spp (17.7%) [10]. A retrospective cohort study in the medical intensive care unit of Chaing Mai University Hospital, Thailand on VAP from January 2005 – December 2009 found that the major associated pathogens were *A. baumannii* (54.3%), *P. aeruginosa* (35.2%), and MRSA (15.1%). Most *A. baumannii* (90.2%) comprised drug-resistant strains [51]. A review by Rajesh Chawla on HAP and VAP in ten Asian countries showed that four most common pathogens of HAP including VAP in nine countries were *Pseudomonas* spp. (15 – 23%), *A. baumannii* (9 – 58.5%), MRSA (5 – 23%), and *K. pneumoniae* (5.8 – 23%); for Philippines, most common VAP pathogens were *Pseudomonas* spp. 42.1%, *K. pneumoniae* 26.3%, and *A. baumannii* 13.1% [52]. A study on pathogens causing nosocomial bacteremia among paediatric patients in a district hospital in Kenya from 2002 to 2009 found that most common isolates were *Escherichia coli* (44/212), *Klebsiella pneumoniae* (43/212), *Staphylococcus aureus* (20/212), *Acinetobacter* spp (19/212), group D streptococci (18/212), and *Pseudomonas aeruginosa* (16/212), these pathogens accounted for three-quarters of nosocomial infections [11]. Recently, a study at nine provincial hospitals in the Northeast of Thailand showed that most common pathogens of hospital-acquired bacteremia in a period from 2004 to 2010 were *Acinetobacter* spp. (501/2101), *Klebsiella pneumoniae* (455/2101), *Staphylococcus aureus* (446/2101), *Escherichia coli* (403/2101), *Pseudomonas aeruginosa* (179/2101), and *Enterococcus* spp. (117/2101) with the rate of multidrug resistance (defined as non-susceptibility to at least one agent in three or more antimicrobial categories) among those pathogens were 75%, 66%, 50%, 63%, 25%, and 3%, respectively [53].

1.4 Risk factors for hospital acquired infection and VAP

WHO data from high income countries, show the most common factors independently associated with HAI occurrence are: older age (> 65 years), admission to an emergency or intensive care unit, hospital stay longer than 7 days, placement of a central venous catheter, indwelling urinary catheter, or an endotracheal tube, undergoing surgery, trauma induced immunosuppression, neutropenia, a rapid or ultimate fatal disease, and coma or impaired functional status [1]. Similar risk factors were identified in low- and middle-income countries (LMIC) with the addition of other risk factors, although not demonstrated as independent risk factors: poor infection control practices, inadequate numbers of trained infection control staff, understaffed hospital unit, and insufficient equipment and supplies [1]. Gravel et al. through multivariate logistic regression analysis for HAI found that ICU admission was not risk factor for HAI but hospital stay > 7 days, having central vascular catheter, tracheal tube, or urinary catheter were independently associated with higher risk for HAI [54].

In addition to the above risk factors for HAI in general, many studies have looked at specific risk factors for VAP. Interpretation and comparison of studies is again hampered by variations in definitions of VAP used and prospective versus retrospective methods of data collection. However several consistent risk factors emerge: duration of mechanical ventilation, increased age and severity of underlying disease, use of muscle relaxants and paralysis. A prospective cohort study for one year (2003 – 2004) on 51 patients ventilated for over 48 hours in a tertiary critical care units in Mumbai, India, by Panwar et al. found that VAP incidence increased along with prolonged duration of mechanical ventilation and higher severity of underlying disease at ICU admission [55]. The nature of the underlying disease is also important, for example in burns patients, VAP developed in 44.6% and 27% of patients with and without inhalational injury, respectively [56]. In a prospective study of trauma patients in Iran, type 2 diabetes was found to be a risk factor for VAP development, associated with a hazard ratio of 10.1 after adjustment for confounders [57]. Charles et al

found that supine head position was significant risk factor for VAP [58]. Liu et al. found that prolonged mechanical ventilation > 4 days and ICU stay > 9 days, and high APACHE II score > 9 points were associated with higher risk for ventilator associated tracheobronchitis in patients > 65 years old [59]. A case control study using electronic database in the United States in 2011 found that mandatory ventilation mode and positive fluid balances were significant risk factors for ventilator associated conditions and commencing benzodiazepines before intubation, total opioid exposures, and paralytic medications were possible risk factors for infection-related ventilator associated complications [60]. A randomized trial evaluated impact of no sedative versus interrupted sedative use on ventilation time on 113 critical ill adult patients ventilated in Odense University Hospital, Denmark, from April 2007 to December 2008 [61]. This trial found that patients with no sedative had statistically significant shorter ICU and hospital stays and lower mortality in ICU than those patients used sedative, but there was no significant difference in VAP incidence between the two groups.

An expert review on HAI conducted in Asian countries specifically considered risk factors for VAP. The following were identified: male sex, preexisting pulmonary disease, multiple organ system failure, the presence of intubation or enteral feeding, mechanical ventilation, and supine position. In addition to these, the panel considered elderly age, APACHE II score > 15 points, previous use of antibiotics for more than 2 weeks, diabetes, immunosuppression, dialysis, reintubation due to failed weaning, use of paralytic sedative, and length of ICU stay to be additional risk factors [52]. However, the data used in this report were often local hospital data without prospective collection or standard definitions and these risk factors were identified by discussion of the panel members, and presented without any statistical analysis. Thus there are relatively few high-quality data on VAP risk factors in Asian and developing countries.

1.5 Impact of hospital acquired infections

1.5.1 Impact of general hospital acquired infection (HAI)

HAI affects a large number of patients every year and is a significant global health problem [4, 6, 10] due to its significant impact on costs, prolonged hospital stay, attributable mortality, and other complications [62-64]. As described earlier VAP is one of the most common HAIs. Based mainly on data from high-income countries, WHO estimates that VAP has an attributable mortality between 7% and 30% and attributable costs at US$ 10,000 – 25,000 per case [1].

European estimates indicate that HAIs cause 16 million extra days of hospital stay, 37,000 attributable deaths annually, and contributed to an additional 110,000 deaths [4]. In the USA, around 99,000 deaths were attributed to HAI in 2002 [6]. Of these, approximately 36,000 were due to pneumonia, 31,000 to BSI, 13,000 to UTI, 8,200 to SSI, and 11,062 to other infections.

The burden of HAI is also reflected in significant financial losses. These infections account for approximately 7 billion euro in Europe, in direct costs alone [4]. The annual economic impact of HAI in the USA was estimated to be approximately 6.5 billion US$ in 2004 [6]. Another report showed that the overall annual direct medical costs of HAI ranged from 28.4 to 45 billion US$ for the United States, and suggested that the benefits of effective infection control interventions can range from 5.7 to 6.8 billion US$ (if 20% of HAI prevented) to as high as 25.0 to 31.8 billion US$ (if 70% of HAI prevented) [65]. Recently, the annual societal burden of HAI in the USA was estimated to be 96 – 147 billion US$ in 2013 [66]. The WHO estimated that overall, for each 100 patients admitted to hospital, 10 patients will develop a HAI [1]. Due to lack of human resources, equipment and inadequate recognition of HAI, the real burden of HAI may be much higher [2]. From available data in 2011 WHO reported that the crude excess mortality in adult patients was 18.5% for CR-UTI, 23.6% for CR-BSI, and

highest at 29.3% for VAP, and increase in length of stay varied between 5 and 30 days for patients with HAI [1]. In Mexican ICUs, the overall average cost of a HAI episode was 12,155 US$ and in Argentina ICUs, the overall extra-cost estimates for CR-BSI and HAP averaged 4,888 US$ and 2,255 US$ per case, respectively [1].

1.5.2 Impact of Ventilator Associated Pneumonia (VAP)

When considering VAP in particular there are conflicting data with many studies using retrospective study designs with increased risk of bias and difficulty in correcting for confounding variables such as length of ventilation or severity of underlying disease. Some well conducted studies reported significant increases in attributed mortality with VAP ranging from 1 to 1.5% [16]. However a retrospective study analyzing data from a large database in the United States did not find a significant difference in mortality between patients with and without VAP [67]. Possibly the best estimate of the mortality impact of VAP comes from an individual patient meta-analysis of 6284 patients from 24 randomized VAP prevention trials by Melsen et al [68]. The use of randomized patient data should eliminate confounding that complicates other study designs. This study found an attributable mortality of 13% and this effect was concentrated in surgical patients and those with mid-level severity scores (APACHE II 20 – 29 points). A recent meta-analysis assessing mortality prediction in patients with VAP evaluated 7 different prediction methods in studies including over 5000 patients but did not find any superior – only some were much more complicated than others [69].

Data from resource-limited settings regarding mortality and VAP are often of poor quality and difficult to interpret. A review by Chawla has suggested that VAP is associated with increased mortality in some ICU settings where 22.5% of Thai patients were reported to die from VAP, in India an attributable mortality of 37% was reported, and in China a study has shown attributable mortality of 14% due to VAP [52].

Irrespective of mortality, most studies have found that VAP is associated with prolonged ICU stay and ventilation time with mean extra hospital cost ranging from 10,000 to 40,000 US$ per VAP case in high income countries [16, 67]. Mathai et al. conducted a study in a tertiary hospital ICU in Northern India between October 2010 to September 2011 found that VAP patients had significantly longer hospital stays compared with patients without VAP (21 vs 11 days) and the attributable cost per VAP case was 5,200 US$ [70]. However, that study found no significant difference in mortality between patients with VAP (68.4%) and without VAP (61.3%), $p = 0.200$. A retrospective study on 621 patients diagnosed VAP in medical ICU in Chiang Mai university hospital from 2005 to 2011 found that mortality was 44.4% [51].

1.5.3 Impact of Ventilator Associated Tracheobronchitis (VAT)

Studies looking at VAT again show conflicting data regarding its effect on outcome and relationship to VAP. A study by Nseir et al. found that in medical ICU, mortality of VAT patients was 38.7% compared with 32.1% in patients without VAT but this difference was not statistically significant [29]. That study also showed that VAP incidence among VAT patients was lower than in patients without VAT, and VAT patients who used antibiotics had significant lower mortality than who were not. In another study, Nseir et al. found that VAT was statistically associated with increase in ventilation time and ICU stay compared without VAT [71]. A prospective observational study of 114 ICUs in Spain, France and South America comparing VAT and VAP in ICU patients found that VAT was associated with a lower mortality than VAP (mortality rate was 29% in VAT compared to 40% in VAP and 30% in those developing no respiratory infection [32]. The authors also compared the use of appropriate antibiotics and found those patients with VAT treated initially with appropriate antibiotics were less likely to ‘progress’ to VAP.

1.6 Management of hospital acquired infections

1.6.1 Prevention of hospital acquired infection

There are many guidelines and interventions to limit and control HAIs (standard barrier precautions, hand hygiene, isolation etc.), specific site infections (hospital acquired pneumonia, ventilator associated pneumonia, central venous catheter related blood stream infection, catheter related urinary tract infection, and surgical site infections), and specific pathogens (multidrug resistant organisms, carbapenem resistant Enterobacteriaceae, MRSA etc.) developed by agencies such as CDC, WHO and some developed countries (Guidelines by CDC available at https://www.cdc.gov/hicpac/pubs.html) [2, 72-78]. Many hospitals in developed countries will have integrated some of these into local guidelines, increasingly spurred on by financial systems and management interventions that penalise healthcare facilities that have high rates of HAI.

Recognising the potential global health problem of HAIs, WHO issued guidelines for prevention of HAIs in 2002 [2]. In 2009, WHO Guidelines on hand hygiene in health care published evidence that good hand hygiene reduced HAIs, although hand hygiene compliance was low, ranging from 5% to 89% with a pooled rate of 38.7% [75]. This guideline also indicated that the reasons for low hand hygiene compliance included lack of hand hygiene guidelines, the opportunities for hand hygiene during patient care, and knowledge about risk for transmission of HAI by healthcare worker's hand. In 2016 WHO has issued an update for guidelines on the core components of infection prevention and control (IPC) programmes at the national and acute care facility level with the main aim being to supply recommendations required to prevent HAIs and combat antimicrobial resistance (AMR) through IPC good practice [72]. This guideline includes eight core components which are Infection prevention and control (IPC) programmes; IPC guidelines; IPC education and training; Surveillance; Multimodal strategies; Monitoring/audit of IPC practices and feedback; Workload, staffing and bed occupancy; and Built environment, material and equipment for IPC at the facility

level. Of which, the six first components are for both national and acute care facility level and two last components are only for acute care facility. Also in 2016, WHO published Guidelines for prevention of surgical site infections [74].

Environmental cleaning has an important role in reducing the reservoir of microorganisms causing HAIs. A review by Otter et al found that there was evidence that the contaminated hospital surface environment played a role in the pathogenesis of hospital acquired infection pathway and that effective cleaning and disinfection of hospital surfaces resulted in a decrease in HAIs [79]. CDC also developed guidelines for environment infection control in healthcare facilities in 2003 [80]. More recently patient mouth care, selective digestive tract decontamination and oral care have also been shown to reduce HAI, although generally in high income settings [81].

Regarding prevention of VAP, CDC had issued Guidelines for prevention of nosocomial pneumonia in 1997 and healthcare-associated pneumonia in 2003 [76, 82]. At present, there are many guidelines developed and issued by CDC, available at https://www.cdc.gov/hicpac/pubs.html [78]. Recently, the Infectious Diseases Society of America and the American Thoracic Society have issued clinical practice guidelines for managements of adults with hospital-acquired and ventilator-associated pneumonia [83]

Many interventions have been postulated to reduce the incidence of VAP: hand-hygiene, body position, subglottic suction tubes, and continuous endotracheal cuff pressure control. Whilst individual components may be deployed, lowered rates of VAP are particularly seen when care bundles consisting of several components are deployed [84]. Many prevention bundles comprising multiple interventions targeting a specific HAI have been developed, implemented universally and been shown to be effective in decreasing HAIs [85-87]. To encourage and improve compliance with such policies, punitive reimbursement has been proposed recently in an attempt to reduce the rate of HAI [88]. This policy compels hospitals to pay for HAI treatment cost, so the hospitals have to raise awareness and enhance methods

to limit HAI including VAP. These measures were mainly implemented in developed countries and the HAI prevalence in those countries has shown a decreasing trend [4, 5]. Even the organization, management, and structure of hospitals have been evaluated for the prevention of HAIs [89]. While in developing countries, the literature about VAP prevention remains limited and the capacity to implement such significant control systems is reduced by lack of resources, understanding of the problem and political will [10].

1.6.2 Antibiotics selection guidelines for HAI and VAP/VARI

HAI treatment varies according to site, severity and the potential pathogens. The HAI treatment can often be difficult because the causative bacteria are commonly highly resistant to antibiotics. This means the antibiotics chosen for HAI are usually very broad spectrum, costly, and may even be more toxic. In settings of high antibiotic resistance the usual choices include anti-Pseudomonal beta-lactams or cephalosporins, carbapenems and colistin sometimes combined with an anti-staphylococcal agent to which local strains (usually MRSA) are susceptible. When empiric treatment for HAI is needed for a critically ill patient it may include a combination of two or more broad spectrum antibiotic agents to cover all potential pathogens because in these situations delays in effective antibiotics therapy may lead to increased mortality parallel with delay time.

Guidelines for VAP management have been developed by organizations in Europe, the United State, Canada, and Asia [77, 83, 90, 91]. The Infectious Diseases Society of America and the America Thoracic Society issued guidelines for management HAP & VAP in 2005 and updated these in 2016. These guidelines recommend that all empiric treatment for suspected VAP in patients with high risk for acquiring multidrug resistant bacteria include antibiotics agents to cover for MRSA, *P. aeruginosa* and other gram negative bacilli [38, 83]. As discussed above inappropriate initial antibiotics may be associated with worse outcome in both VAP and VAT however due to large variations in local resistance patterns there are significant limitations on the value of national or even regional guidelines. Unfortunately the

use of broad spectrum agents is likely to drive antimicrobial resistance to the point where there are no effective antibiotics for common bacteria. Thus it has been proposed that the best way to manage these infections is to combine treatment with effective prevention methods and antimicrobial stewardship to limit overuse of broad spectrum antibiotics and reduce the impact on antimicrobial resistance (AMR) due to selective pressure. A 2013 meta-analysis concluded that there was no difference in short versus long courses of antibiotics in terms of outcome or relapse rate, although there was a strong trend towards reduced relapse rate with long-course antibiotic [92]. More recently shorter courses of antibiotics for VAP treatment have been proposed, and are widely adopted particularly in developed countries [93].

The value of any VAT treatment had been questioned for a long time. However recent evidence is that there is benefit from treatment – reducing the progression to VAP and improving outcome. However as some authors maintain that most VAT will not progress to VAP and may have no effect on outcome then the use of broad spectrum antibiotics for its treatment remains controversial [18, 33, 94, 95]

1.7 Antimicrobial use in intensive care units

ICUs are significant utilizers of antibiotics. Antibiotic use can be presented in terms of daily defined doses (DDDs) to allow comparison between different antibiotics and across sites. Meyer et al reported that antimicrobial consumption in 40 German ICUs from 2001 to 2004 ranged from 427 to 2798 defined daily doses (DDD)/1000 patient days with median 1351 DDD/1000 patient days. There was no statistically significant change in total antimicrobial use over period from 2001 to 2004 [96]. A report by Hohn et al. showed that antimicrobial consumption in a surgical ICU of a 500 - bed hospital in Germany was 1005.0 DDD/1000 patient days in 2010, decreased to 935.5 in 2011 then to 791.9 DDD/1000 patient days in 2012 after an intervention using procalcitonin level as a guide for stopping antimicrobial use in 2011 [97]. A point prevalence survey by ECDC between 2011 – 2012 in European hospitals showed that antimicrobial use was highest in ICUs with 56.5% of ICU patients

using antimicrobials on the surveyed day and 37.3% of the total antimicrobial agent use in ICUs was for hospital acquired infections [5]. Magill et al. conducted a one day prevalence study at 183 hospitals in 10 states of the USA between May and September 2011 and also found that prevalence of antimicrobial use was highest in ICU patients (57.7%) compared with patients on other wards (48.6%) [98]. Dulhunty et al. reported on antimicrobial use in 37 ICUs of Australia and New Zealand in May 2007 from a one day point prevalence survey, finding that among 422 patients in the ICUs, 195 patients (46%) were using antimicrobials for the treatment of infection, 104 patients (25%) for prophylaxis, and 123 patients (29%) used no antimicrobials [99]. There were 331 antimicrobial agents used for 225 infections in 193 patients, so on average one patient received 1.7 antimicrobial agents. The most common infections were at respiratory tract (39.5%), abdominal 12.8%, and blood stream 12.3%.

There are limited data on antimicrobial use in intensive care units in low and middle income countries. Sharma et al. conducted a prospective study on antimicrobial consumption in the ICU of a tertiary hospital over four months in 2008 in New Delhi, India, found that the total antimicrobial consumption was 2320 DDD/1000 patient days [100].

1.8 Hospital acquired infections in Vietnam

1.8.1 Introduction the Vietnamese healthcare system

In 2014, the population of Vietnam was 90,728,900 individuals, with a proportion of males 49.33%. It is a relative young population with a median age of 29 years, with 31.3% of the population below age of 20 years and 10% ≥ 60 years [101]. By comparison the UK population in the same year was 64,596,752 with 23.1% aged 60 years and above and 23.6% under the age of 20 years [102]. World bank figures show that Vietnam spends 7.1% of gross domestic product (GDP) on healthcare (compared with an LMIC average of 4.5% and 9.1% in the UK), per capita healthcare spending was 142 USD (compared with an LMIC average of 90 and 3,935 in the UK) [103].

The government healthcare system includes 48 tertiary hospitals (31,777 beds), 458 provincial hospitals (115,006 beds), 1,191 district hospitals (77,744 beds), 11,101 communal healthcare stations (49,666 beds), and 758 other branches hospitals (6,020 beds). Besides the government system, there were 169 private hospitals (11,762 beds). There were 7.8 doctors, 10.8 nurses, and 25.6 beds per 10,000 population. Health insurance coverage within the population was 71% and life expectancy 73.2 years. Bed occupancy rate at central, local, and other branches were 119.1%, 112.0%, and 104.3%, respectively [101]. By comparison European Union official statistics cite figures of 27.9 physicians per 10,000 population for the UK and 22.7 beds per 10,000 population in 2014 [104], with average overnight bed occupied rate of 89.4%, ranged from 65.8 to 98.7% in acute and general hospital in the UK in December 2014 [105].

The Vietnam Ministry of Health categorises hospitals to area served (tertiary, provincial, and district hospitals) and technical levels (sequentially from highest to lowest technical level: extra, I, II, III and IV). Tertiary or national hospitals are reference hospitals for other tertiary, provincial, and district hospitals; provincial hospitals are mainly references for district hospitals in the same province; and district hospitals offer healthcare for the population in the same districts. The technical level of hospitals are depending on their score according to the evaluation system of the Ministry of Health [106]. The number of staff in government hospital is regulated by a Circulation of the Ministry of Health and Ministry of Home Affairs [107]. According to that document, the total staff in government hospitals depends most on the technical level of the hospital and the total number of beds. The maximum ratio of staff number per bed is 2.2 for the highest-level hospitals and 1.0 for level IV hospitals. The proportion of staff in different roles is distributed as follows: medical 60 – 65%, paramedical 15 – 22%, and administrative section 18 – 20% of total staff in hospital. There are no specific regulations concerning staffing of intensive care units (ICU).

The operation of the healthcare system is based mainly on the official catchment area of the hospital. Community stations serve mainly for public health programmes and a variety of basic healthcare services and they are not categorized as hospitals. The majority of primary care occurs in the district level hospitals. There is a significant difference in capability and available medical equipment between district hospitals and provincial hospitals, and also between provincial and tertiary hospitals. The Ministry of Health reported that equipment at district and provincial hospitals was commonly inadequate, that district hospitals were supplied only 30 – 50% of total equipment needed, and were not able to implement 27.9% of total healthcare services which were designated [108]. Similarly, provincial level hospitals were not able to do 3.2% - 24.1% of total healthcare service procedures that they were designated to. If patients require more care than what can be delivered by the district level hospital to which they are admitted, they will be transferred to the provincial level hospital or to tertiary (national) hospitals, these hospitals are usually level I or higher. Given the under provision of resources in the district and provincial level hospitals, this may lead to an overload of the tertiary hospitals, while provincial and district hospitals operate below capacity. However, health statistics for 2014 showed that bed occupancy rate was more than 110% in both provincial level hospitals (112.0%) and tertiary level hospitals (119.1%) [101].

A study into the needs for influenza pandemic preparedness showed that there was a shortage of ventilators in all provincial and city hospitals in every province of Vietnam, with most provinces lacking more than 3 ventilators per 100,000 population [109]. These data indicate that the need for healthcare of the population is much more than the capacity of the health care system. This lack of resources may mean that there is reduced time to clean equipment between patients and those requiring facilities such as mechanical ventilation may receive it later, or for shorter durations than may otherwise be preferable. Staff have to care for increased numbers of patients, with fewer nurses or doctors for each patient. These factors mean that particularly in resource intense environments such as ICU, there could be increased

adverse events in hospitals including HAIs or that the impact of these may be more serious compared to better resourced settings

1.8.2 Hospital acquired infections in Vietnam

Data concerning HAIs are very limited in Vietnam as there is no national surveillance system for HAI in general or VARI/VAP in particular. Among the few HAI studies reported from Vietnam, most were done in surgical departments and focused on surgical site infections [10]. A large study of HAI performed in 2008 in 36 hospitals (in 14 provinces including two teaching, 18 provincial, and 16 district hospitals) with a total sample size of 7571 patients (354 ICU patients, accounting for 4.7%) showed an overall HAI prevalence of 7.8% with HAI incidence density of 8.3 episodes per 1000 patient-days [110]. This study found that the most common HAIs were pneumonia and surgical site infection, accounting for 41.9% and 27.5% of total HAIs respectively and the highest prevalence of HAI was in ICU with 23.7% (84/354) of ICU patients suffering from HAI at the time of the survey. Pham Duc Muc et al. carried out a point prevalence study on HAI at 19 hospitals (4 tertiary and 15 provincial) in 2005, showing that 5.7% (535/9345) patients had at least one HAI and the prevalence of HAI was 6.0% (559/9345) [111]. Another point prevalence survey at Bach Mai Hospital (a large tertiary referral centre in Northern Vietnam) in October 2006 showed that 5.7% (77/1354) patients had HAI at the time of the survey and the prevalence of HAI was 5.9% (80 HAIs/1354 patients), the most common HAIs were respiratory tract infections accounting for 75% (60/80) of HAIs, urinary tract infection 10% (8/80), and digestive tract infection 5% (4/80) [112]. The highest prevalence of HAI was 31.3% (15/46) in ICU and most frequent cause of HAI were *Pseudomonas aeruginosa* 28.6% (6/21), *Acinetobacter baumannii* 23.8% (5/21), *Klebsiella pneumoniae* 19.0% (4/21), and candida 14.3% (3/21). In a specialist tetanus ICU in Southern Vietnam, a randomized controlled trial compared incidence of hospital-acquired pneumonia in supine and semirecumbent positions and reported incidence of HAP of 20.8% and 25% in each arm respectively [113]. Some other studies on HAI in Vietnamese

ICUs have shown that the point prevalence of HAI in ICUs ranged from 19.3% to 31.3% [110, 112, 114-117].

1.8.3 Ventilator-associated pneumonia in Vietnam

Truong Anh Thu and colleagues reported a pooled incidence density of VAP of 34.7 episodes per 1000 ventilation days at three departments with ventilated beds (ICU, Emergency department, and the toxicology center) in Bach Mai Hospital in the period 2002 to 2003, incidence density was the highest in the ICU (61.3 episodes per 1000 ventilation days) [116]. This study also reported that the most common microbial isolates associated with HAI in ICU were *A. baumannii* 28.1% (34/121), *P. aeruginosa* 25.6% (31/121), *Candida* spp 14% (17/121), *K. pneumoniae* 10.7% (13/121), and *Escherichia coli* 7.4% (9/121).

In an earlier observational prospective study on 92 patients ventilated for over 48 hours in the intensive care unit in National Hospital for Tropical Diseases (a tertiary referral hospital for infectious diseases) in 2012, VAP prevalence was 17.4% and an incidence density of VAP was 11.7 episodes per 1000 ventilation days [118]. A retrospective study on all patients admitted to Intensive Care Unit in Bach Mai Hospital from September 2008 to April 2009 for more than 48 hours found that 90/477 (18.9%) patients developed VAP during their stay, with a VAP incidence density of 27.4 episodes per 1000 ventilation days [119]. This study also showed that the most common isolates from hospital-acquired pneumonia were *A. baumannii* 44.7% (59/132), *Candida* spp. 19.7% (26/132), *P. aeruginosa* 17.4% (23/132), and *K. pneumoniae* 5.3% (7/132). The carbapenem resistance rate was considerable, with resistance in 90.7% (49/54) of *A. baumannii* and 68.4% (13/19) of *P. aeruginosa,* and one isolate of *A. baumannii* resistant to colistin with minimum inhibitor concentration (MIC) > 4 mg/L. A large multisite surveillance study on hospital-acquired infections (HAI) in intensive care units of 14 tertiary and provincial hospitals across Vietnam in 2013, performed as part of this PhD, has shown that the pooled prevalence of HAI was 29.5%, of which hospital-acquired pneumonia accounted for ~ 80% (chapter 3 [120]). In this study, the most common isolates

from HAI were *A. baumannii* 24.4% (177/726), *P aeruginosa* 13.8% (100/726), and *K pneumoniae* 11.6% (84/726) with carbapenem resistance rate of 89.2%, 55.7%, and 14.9%, respectively.

Recently, Tran Huu Thong and colleagues reported a randomized control trial of 153 patients (76 in control group and 77 in interventional group) to evaluate the impact of continuously subglottic suction on VAP (using CPIS and microorganism criteria for VAP diagnosis) at Bach Mai hospital from 2009 to 2013 and showed that the incidence of VAP was 56.6% in conventional group and 39.0% in the interventional group (continuously subglottic suction) [121]. This study showed that the most common bacteria associated with VAP were *A. baumannii* 49.3% (36/73), *K. pneumoniae* 15.1% (11/73), and *P. aeruginosa* 11% (8/73) with carbapenem resistance rates of 75%, 15%, and 10%, respectively.

The high level of carbapenem resistance among bacteria commonly associated with VAP and HAI in Vietnamese ICUs necessitates the use colistin, an antibiotic of last resort, with questions surrounding its dosing, efficacy, and toxicity. A study on population pharmacokinetics of colistimethate and formed colistin in adult critical ill patients at four institutions in three countries (USA, Thailand, and Greece) found that only 65% to 75% of patients with creatinine clearance ≥ 80 ml/min achieved target average plasma concentration with intravenous colistin dosage recommended by the US Food and Drug Administration and European Medicines Agency [122]. Trifi et al. found that a high dose of colistin (a loading dose of 9 MIU then a maintenance dose of 4.5 MIU every 12 hours) was associated with better activity without nephrotoxicity [123]. Dewan et al. also found that high dose of colistin in critical ill patients was not associated with significant risk of nephrotoxicity [124]. Whereas, other studies have shown that nephrotoxicity was associated with a higher dose of colistin [125-127].

1.9 Summary and purpose of the thesis

HAI and particularly VAP are important problems throughout the world. Data suggest that they may be even more important in developing countries but there are sparse and poor quality data regarding them in these settings. This data however is vital for targeting resources appropriately to reduce the burden of these infections and to combat the threat of antimicrobial resistance.

Currently there are some data suggesting that the burden of HAI and VAP is relatively high in intensive care units in Vietnam. Therefore, this thesis is intended to address this issue, providing high quality data to inform future policy in Vietnam.

The objectives of this thesis are:

1. Assess the prevalence of hospital acquired infections at ICUs of 14 hospitals across Vietnam.
2. Quantify and describe antibiotic use in the ICUs of 14 hospitals across Vietnam.
3. Assess the etiology, resistance pattern, associated antibiotic use and outcome of ventilator associated pneumonia (VAP) in three hospitals in Vietnam.

To this end I, with the help of a team of research & clinical staff, carried out a point prevalence survey of HAI and antibiotic use in the ICUs of 14 tertiary and provincial hospitals across Vietnam and conducted an observational study to assess systemically the epidemiology, bacterial etiology, antibiotic use, and clinical outcome of VAP at three referral hospitals in Hanoi and Ho Chi Minh City, Vietnam. Such data is urgently needed to inform optimal management, prevention, antimicrobial stewardship and infection control to reduce HAI, particularly VAP in ICUs in Vietnam and potentially other low resource settings.

Chapter 2

Material and Methods

This chapter described the study setting, design aims, data collection, and data analysis for two studies in the thesis with the results were presented in next four chapter.

2.1 Methods for chapter three and four

2.1.1 Study aims, design and settings

We conducted a repeated point prevalence survey (PPS) to determine the prevalence of HAIs and to assess antimicrobial use and antimicrobial resistance using the methodology developed by the European Center for Disease Prevention and Control (ECDC) [14]. The study was conducted on one day each month from October 2012 through September 2013 on 15 adult ICUs of 14 hospitals at provincial level (n = 8) or higher (n = 6), throughout Vietnam. These hospitals represent the main teaching hospitals in different parts throughout Vietnam (Figure 2 - 1). In the study, names of hospitals were coded with different numbers with ordinal number on the map (Figure 2 – 1).

ICUs were chosen as the initial focus because this is an area where bacteria associated with hospital acquired infection were seen to be resistant to most available antibiotics, and ICU doctors are familiar with the problems HAI present and the definitions used to categorise the infections.

Training for the project was organised centrally (in Hanoi and Ho Chi Minh City): four workshops covered training in the protocol and data collection, and use of the survey software to input and export data for electronic transmission to the project statistician. The study team visited each participating ICU to inventory capacity and help local study doctors to implement the protocol and use HAI definitions correctly.

The survey doctors were assigned at each site, usually a member of staff at the ICU, to received training on ECDC definitions of HAI and the study protocol.

The software for data management was developed from the ECDC developed software HelicsWin.Net version 1.3 [128].

Additional laboratory training and microbiology capacity development was conducted to ensure that identification and susceptibility testing of bacteria was performed to a sufficiently high and uniform standard. Laboratories were given Vietnamese translated versions of the Clinical and Laboratory Standards Institute guidelines (CLSI) for antimicrobial susceptibility testing and were enrolled in an external quality assurance program for identification and drug susceptibility testing (The United Kingdom National External Quality Assessment Service (UK NEQAS) for Microbiology) [129]. Training included central workshops and visits to the site laboratories at the start and during the project.

Each ICU received a laptop with the required software installed and Vietnamese instructions. Every month, after the survey was completed, data were entered into the database software and sent to the study statistician and coordinator. These data were then checked for missing and outlying values for feedback to the site study doctors for further checks. The final data were extracted to a SPSS database for final analysis.

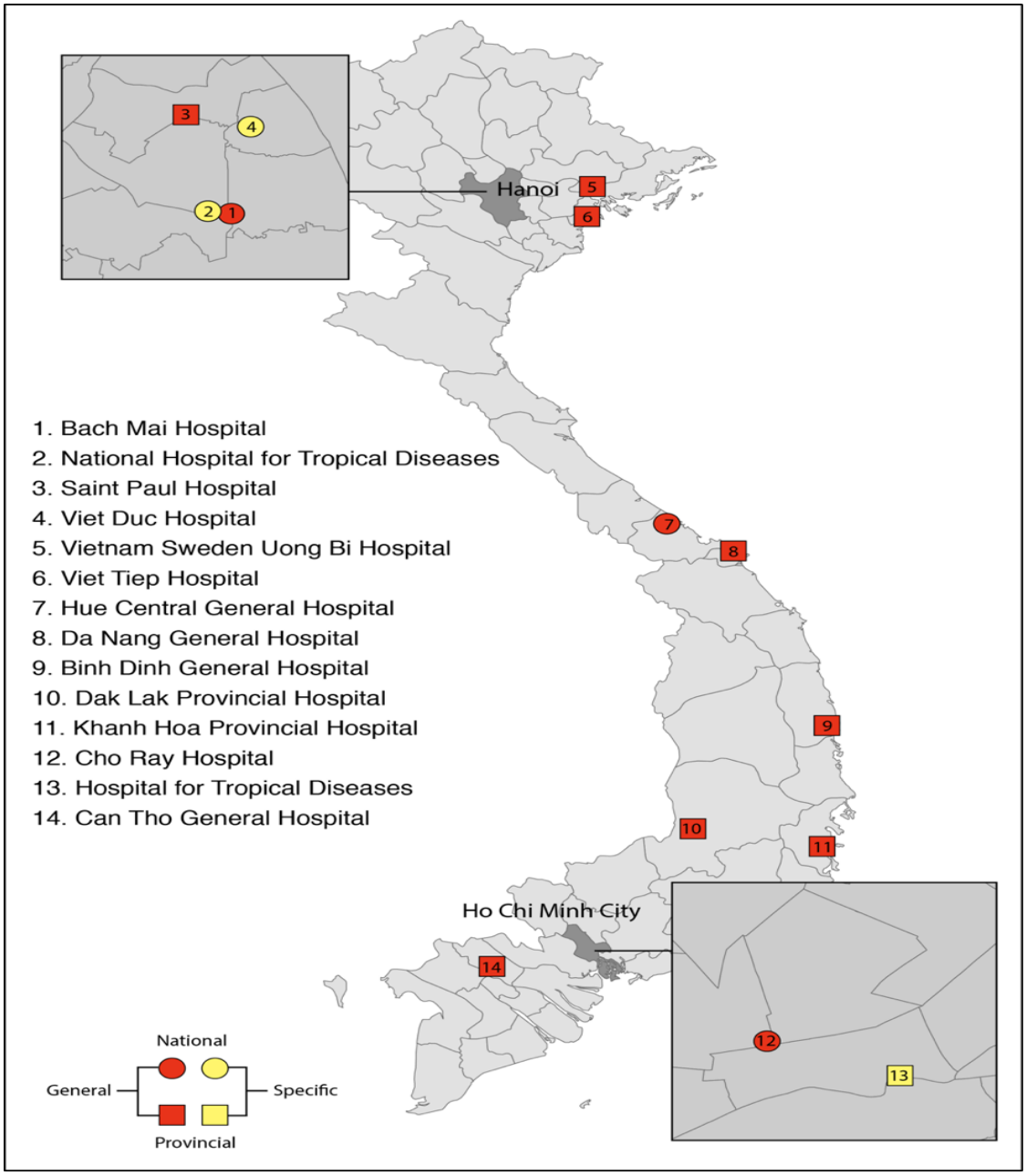


Figure 2 – 1. Location of the participating hospitals

2.1.2 Hospital and ICU resources

The surveyed hospitals included three specialty hospitals, one for surgery (H05, tertiary) and two for infectious diseases (H01 - tertiary and H15 - province). H02, H10, H13 and H16 are large tertiary general hospital in the North (H02), Middle (H10), and the South (H13 and H16), respectively. The other hospitals are provincial level general hospitals. Basic information on study settings was presented in Table 2 – 1.

Table 2 - 1. Basic information on study sites

Participating Hospitals					Participating ICU	
Hospital code	**Hospital name**	**Location**	**Type of hospital**	**Size (beds)**	**Specialty**	**Size (beds)**
H01	National Hospital for Tropical Diseases	Hanoi City	Tertiary – Infection specialty	280	Infection	18
H02	Bach Mai Hospital	Hanoi City	Tertiary - General	1900	General	38
H04	Saint Paul Hospital	Hanoi City	Provincial – General	800	Medical	20
					Surgical	17
H05	Viet Duc Hospital	Hanoi City	Tertiary - Surgical specialty	1050	Surgical	16
H06	Viet Tiep Hospital	Hai Phong City	Provincial – General	900	Medical	16
H07	Vietnam Sweden Uong Bi Hospital	Quang Ninh	Provincial – General	750	General	10
H08	Binh Dinh General Hospital	Binh Dinh	Provincial – General	1050	Medical	20
H09	Da Nang General Hospital	Da Nang City	Provincial – General	1500	General	47
H10	Hue Central General Hospital	Hue City	Tertiary – General	2300	Medical	60
H11	Khanh Hoa Provincial Hospital	Khanh Hoa	Provincial – General	1000	Medical	34
H12	Dak Lak Provincial Hospital	Dak Lak	Provincial – General	750	General	20
H13	Cho Ray Hospital	Ho Chi Minh City	Tertiary – General	1800	General	31
H15	Hospital for Tropical Diseases	Ho Chi Minh City	Provincial - Infection specialty	550	Infection	23
H16	Can Tho Central General Hospital	Can Tho City	Tertiary – General	800	General	30

2.1.3 Data collection

Data collection comprised two areas: baseline data and point prevalence survey (PPS) data.

2.1.3.1 Study settings baseline data

Baseline data were collected form all sites at the beginning of the study. All participating hospitals provided data on basic infrastructure and infection control indicators at the beginning of the study. Baseline data included total number of beds, rooms, single bed rooms, number of doctors and nurses at the ICUs, admissions per year, patient days per year, alcohol hand rub consumption, and availability of alcohol hand rub at ICU bed. These data were

collected by the survey doctors from the respective general planning departments and infection control departments.

2.1.3.2 Patient Data

Patient data were collected monthly through point prevalence survey from each ICU. These data were collected by the survey doctors in discussion with the treating team and review of relevant clinical diagnostics results (radiology/microbiology).

Patient selection

Patients aged ≥ 18 years, admitted to participating ICUs before 8 a.m. on the survey day, and remaining there during at the survey time were included.

Patient data collection

The following data were collected: origin of patient before admission to ICU (e.g. community, other ward in the same hospital, inter-hospital transfer), primary reason for ICU admission, relevant comorbidities, currently deployed interventions (eg intubation, central venous catheter), presence of active HAI, results of routine microbiological investigations, antimicrobial agent use, and involvement of patient's family in patient care. All data were collected as in case record form (CRF), presented in section B – 1 Appendix B, according to definitions in the ECDC PPS protocol [14], with the exception of origin of patient before admission to ICU, primary reason for ICU admission, involvement of patient's family in patient care. These are specified below.

Origin of patient before admission to ICU, was recorded as (1) other hospital, if the patient was treated in another hospital and then transferred to the current ICU; (2) community, if the patient entered the hospital as an emergency case (either directly to ICU or via the emergency department or other department if less than 24 hours from hospital admission), searched intensive care themselves or were transferred from an outpatient clinic; (3) operation room/recovery, if the patient had had surgery and was transferred directly from the operation

or recovery room; or (4) intra-hospital, if the patient was transferred from another department (including emergency department) within the same hospital to the ICU in ≥ 24 hours from hospital admission.

The primary reason for ICU admission was recorded as (1) elective surgery, if the patient has gone through an elective surgical procedure, e.g gastric-cancer surgery, and then been admitted to the ICU; (2) emergency surgery, if the patient has gone through or is awaiting acute surgical intervention, e.g appendicitis, bowel perforation, acute limb ischaemia; (3) trauma, if the patient was admitted after a trauma regardless of whether surgery was indicated, e.g. traffic accident, fall, physical violence etc. If a patient was admitted after trauma and emergency surgery was required, the trauma option was selected; (4) communicable diseases, all infectious diseases caused by microorganisms including bacteria, viruses, fungi and parasites; or (5) non-communicable disease, all other medical, non-infectious diseases.

The following comorbidities were recorded: insulin-dependent diabetes mellitus, COPD on medication, active malignancy (this does not include benign or previously cured cancers), renal failure (creatinine level > 300 μmol/L prior to admission), active HBV/HCV with elevated transaminases, stroke, alcohol abuse as determined by doctor (ideally treating doctor but if not available doctor completing PPS), tetanus, induced immunosuppression, and HIV infection.

Antibiotics use was measured by day of therapy (DOT) which was defined as the sum of all days on each antibiotic agent the patient used calculated for 100 patient days (e.g. if a patient used two antibiotics drugs per day for 2 days, the total antibiotics days were 4 DOT/2 patient days, this equal to 200 DOT/100 patient days) [130]. Both DOT/100 patient days and defined daily dose (DDD)/100 patient days are used to measured antibiotics consumption, although they are not the same. DOT is real antibiotic dose patient used which could be different from patient to patient due to differences in renal or liver function and patient's weight. Whereas,

DDD is calculated for each drug by converting from the amount of antibiotic patients used to the DDD which have been already established and not changed for each drug by WHO [131].

Microbiological results relevant to the current HAI taken on or before the survey day were collected. The results of these tests must be available within two weeks of the survey. Specify up to three isolated microorganisms for each HAI.

Microbiology quality assurance

All laboratories of 14 hospitals were assessed on how they complied with the CLSI guidelines of susceptibility testing to ensure they use updated CLSI guidelines. The participating laboratories were supplied a high quality Vietnamese translation of the most recent CLSI guideline and we ensured that subsequent updates were translated in the future and distributed. The assessment included analyses of distribution of zone diameters in relation to breakpoints used in order to detect erroneous results. Assessment also included an analysis of susceptibility data they provide the clinicians and check these for appropriateness and inconsistencies. During the study period, the laboratories were enrolled in an External Quality Assurance (EQA) program organized by the United Kingdom (NEQAS) to monitor their progress. This EQA programme provided them bacterial isolates 12 times per year they need to identify according to standard methods at each laboratory and to perform susceptibility testing and report back to NEQAS. If sites failed to identify EQA isolates or susceptibility they were visited by our support team on microbiology for further training. Unfortunately it was not possible to save isolates for repeat culture and susceptibility testing as a further quality assurance measure.

2.1.4 Statistical analysis

For descriptive statistics, percentage, frequency, mean, and median values and 95% confidence interval (95% CI) or interquartile ranges (IQR) were calculated as appropriate. The odds ratios of risk factors for developing HAIs in ICU were calculated using data from

the first PPS enrolment of patients who had no HAI on ICU admission. After univariate analysis, all HAI risk factors were used in the multivariate logistic regression models and adjusted for the hospital sites. IBM SPSS Statistics software (version 22 IBM, California, USA) was used for data analysis. P-values < 0.05 (two-sided) were considered statistically significant.

2.1.5 Ethics

The Ethical Committee of the National Hospital of Tropical Diseases (27/HDDD-NHTD) approved the study protocol and waiving of informed consent as the data were anonymous and collected for surveillance purposes and no intervention was conducted. The study was also approved by the Vietnamese Ministry of Health (4921/QD-BYT).

2.2 Methods for chapter five and six

2.2.1 Study Design, aims and settings

A prospective, observational study of the clinical epidemiology and etiology of ventilator associated respiratory infections was performed from November 2013 to May 2015 on the intensive care unit of the National Hospital for Tropical Diseases (NHTD), Hanoi, from July 2014 to May 2015 on the ICU of Bach Mai Hospital (BMH), Hanoi, and from October 2014 to November 2015 on the ICU of Hospital for Tropical Diseases (HTD) in Ho Chi Minh City, Vietnam.

The aims of the study were to assess the etiology, resistance, antibiotics use and outcome of ventilator associated pneumonia (VAP) in three hospitals in Vietnam

NHTD is a national tertiary hospital, specialised in infectious diseases in Hanoi. BMH is a large tertiary general hospital in Hanoi. HTD has the official status of a provincial hospital, specialised in infectious diseases, but it serves as a tertiary referral hospital for infectious diseases for the Southern provinces of Vietnam. NHTD and HTD only admit patients with

infectious disease diagnoses, whereas BMH admits patients with all diagnoses. Basic information of these hospitals and their participating ICUs were presented in Table 2 – 1 with NHTD, BMH, and HTD were coded H01, H02, and H15, respectively.

2.2.2 Inclusion procedure

All patients admitted to the ICUs of participating hospitals were recruited if they met the following inclusion criteria: aged ≥ 18 years for NHTD and BMH, and age ≥ 16 years for HTD, admitted to participating ICU within the previous 48 hours, intubated or on tracheostomy with clear date of intubation and no suspicion or diagnosis of VAP at the time of enrolment. Eligible patients were approached for written inform consent form. Only patients having written inform consent form were enrolled to the study.

All patients received standard of care according to local hospital practice. Once consent was obtained, patients were given a study number. Deidentified numbers were used on all labels, case record forms and the database in order to protect the patient's identity.

Data were collected in a standardized case record form (CRF, section B - 2 in Appendix B) including general demographics, comorbidities, reason for current admission, prior antibiotic use and laboratory and clinical data to establish severity scores (APACHE II in Table 2 – 2 and SOFA in Table 2 – 3).

Table 2 – 2. Acute Physiology and Chronic Health Evaluation (APACHE II) [132]

Parts	APACHE II SCORING SYSTEM									
A: acute physiological score	Variable	+4	+3	+2	+1	0	+1	+2	+3	+4
	Temperature	≥ 41	39-40.9		38.5-38.9	36-38.4	34-35.9	32-33.9	30-31.9	≤ 29.9
	Mean Arterial BP	≥ 160	130-159	110-129		70-109		50-69		≤ 49
	Heart Rate	≥ 180	140-179	110-139		70-109		55-69	40-54	≤ 39
	Respiratory Rate	≥ 50	35-49		25-34	12-24	10-11	6-9		≤ 5
	A-aPO_2 (If FiO_2> 50%) PaO_2 (If FiO_2 < 50%)	≥ 500	350-499	200-349		< 200 > 70	61-70		55-60	< 55
	Arterial pH [1]Serum HCO_3^-	≥ 7.7 ≥ 52	7.6-7.69 41-51.9		7.5-7.59 32-40.9	7.33-7.49 23-31.9		7.25-7.32 18-21.9	7.15-7.24 15-17.9	< 7.15 < 15
	Serum Na^+	≥ 180	160-179	155-159	150-154	130-149		120-129	111-119	≤ 110
	Serum K^+	≥ 7	6-6.9		5.5-5.9	3.5-5.4	3-3.4	2.5-2.9		< 2.5
	Serum Creatinine	≥ 3.5	2-3.4	1.5-1.9		0.6-1.4		< 0.6		
	Hematocrit	≥ 60		50-59.9	46-49.9	30-45.9		20-29.9		< 20
	WBC Count	≥ 40		20-39.9	15-19.9	3-14.9		1-2.9		< 1
	Score = 15 – Actual Glasgow Coma Score (GCS) =									
B: Age adjustment	< 44 = 0 point, 45 – 54 = 2, 55 – 64 = 3, 65 – 74 = 5, > 75 = 6 points									
C: Chronic health adjustment	History of any: Biopsy proven cirrhosis, New York Heart Association Class IV, Severe COPD (e.g., hypercapnia, home O_2, pulmonary hypertension), Chronic dialysis, Immune compromised; then add 2 points for non-surgery or elective surgery and 5 points for emergency surgery.									
Total APACHE II = A ( ) + B ( ) + C ( ) =										

[1]Use only if no artery blood gas test available

Table 2 – 3. The Sequential Organ Failure Assessment (SOFA) Score [133]

	SOFA Score				
Variables	**0**	**1**	**2**	**3**	**4**
Respiratory: PaO_2/FiO_2 mmHg	> 400	≤ 400	≤ 300	≤ 200*	≤ 100*
Coagulation: Platelets x $10^3/\mu L$	> 150	≤ 150	≤ 100	≤ 50	≤ 20
Liver: Bilirubin, µmol/L	< 20	20 - 32	33 - 100	101 - 203	> 203
Cardiovascular: Hypotension	No hypotension	Mean artery pressure < 70 mmHg	Dop ≤ 5 or dob any dose#	Dop > 5, epi ≤ 0.1, norepi ≤ 0.1#	Dop >15, epi > 0.1, norepi > 0.1#
Central nervous system: Glasgow coma score scale	15	13 - 14	10 - 12	6 - 9	< 6
Renal: Creatinine, µmol/L	< 106	106 - 168	169 - 300	301 - 433	> 434

Norepi: norepinephrine; Dob: dobutamine; Dop: dopamine; Epi: epinephrine

* Values are with respiratory support

Adrenergic agents administered for at least 1 hour (dose given in µg/kg per minute)

2.2.3 Ongoing Assessments

Enrolled patients were followed up until 28 days after enrolment or until 28 days after a diagnosis of VAP. A daily record was made by study staff, supervised by myself (NHTD ICU) or local study investigators (Bach Mai ICU & HTD ICU), or study investigators themselves on the CRF. The data collected daily included: intubation & ventilation status, use of paralytic agents or sedation, minimum and maximum temperature over the 24 hours, minimum positive end expiratory pressure (PEEP) and fractional inspired oxygen (F_iO_2) over the 24 hours, changes in sputum production and any results of blood white cell counts and sputum microscopy (see microbiology below). Use of antibiotics and antifungals was recorded, as was the rationale (indication) for the use of any new agents.

Where patients met criteria for VAP investigation (ventilator associated condition [23], i.e. patients had respiratory stability or improvement on ventilator by stable or decreasing daily minimum of F_iO_2 or PEEP for $\geq$ two calendar days then had indicators of worsening oxygenation by increase in daily minimum $F_iO_2 \geq 0.15$ or PEEP value ≥ 2.5 cmH_2O for $\geq$ two calendar days), the following data were recorded: presence of systemic signs or pulmonary secretion, commencement of antibiotics or taking of chest x-ray as per the below. The evaluation included taking of a tracheal aspirate for Gram staining, culture and susceptibility testing; taking of blood culture; and taking blood for assessment of clinical and laboratory parameters necessary for the recalculation of the SOFA score [133].

2.2.4 Endpoints

The primary endpoint was the incidence of VAP using VAP criteria as published by the US Centers for Disease Prevention and Control (Atlanta, GA [USA]) 2008 and 2013 [13, 23] within 28 days of enrollment. The criteria for an endpoint diagnosis of VAP were: 1) deterioration in ventilation following a period of stability: $\geq$ 2 days of stable or decreasing daily minimum PEEP followed by a rise in daily minimum PEEP of ≥ 2.5 cm H_2O, sustained

for ≥ 2 calendar days OR ≥ 2 days of stable or decreasing daily minimum F_iO_2 followed by a rise in daily minimum F_iO_2 of ≥ 0.15 points, sustained for ≥ 2 calendar days) AND 2) systemic signs: fever of > 38 °C or <36°C OR WBC > 12 x 10^9/L or < 4 x 10^9/L) AND 3) radiological signs of pneumonia or clinician commencement of therapy: consolidation, or cavitation on chest radiography OR clinician starts antibiotics for lower respiratory tract infection within a window period of 2 days before the deterioration in ventilation to 2 days after AND 4) pulmonary secretions: increased/new purulent tracheobronchial secretions OR ≥ 25 neutrophils per low power field (100 objective) on Gram stain of endotracheal aspirate.

Additionally, the incidence of VARI (ventilator-associated respiratory infections) was assessed, which included VAP and patients with the following criteria: 1) clinical increased sputum or purulent sputum by microscope examination (≥ 25 neutrophils per low power (x100) field on Gram stain of endotracheal tube aspirate) AND 2) fever of > 38 °C or <36°C OR WBC > 12 x 10^9/L or < 4 x 10^9/L AND 3) clinician starts antibiotics within 2 days after symptom developed.

VARI thus includes VAP, ventilator associated tracheobronchitis (VAT) and pneumonia (as evidenced by chest X-ray), not meeting the study VAP criteria (last two named 'other VARI').

Other secondary endpoints included: 1) 28-day mortality (after enrolment, or in the case of VAP patients at 28 days after diagnosis of VAP); 2) length of ICU and hospital stay; 3) duration on mechanical ventilation; 4) VAP incidence in patients with and without tracheostomy; 5) appropriateness of VAP empiric antibiotic treatment defined as microorganisms isolated from lower respiratory tract sample susceptible to at least one of antibiotics used in empiric therapy; 6) antibiotic use measured by day of therapy (DOT), which was defined as the sum of all days on each antibiotic agent used together for 100 patient days; 7) ICU cost was calculated based on total hospital fee for whole ICU stay period (including all expenditure for medicine, healthcare service, single use medical equipment,

ICU bed day fee, these were included in hospital bill that was collected by research team for each participant), which did not include patient meals, expenditure for family member who stayed with patient or society expenditure; and 8) the microbiological etiology of VAP as determined by culture of endotracheal aspirates.

2.2.5 Microbiology evaluation

Microbiological analysis was performed by the respective hospital microbiology laboratories, as per standard procedures. All hospitals were participating in an external quality assurance programme at the time (UK NEQAS, UK).

Briefly, in patients investigated for VAP, 5-10 mls of blood in a single bottle of aerobic culture media (Bactec, Bekton Dickinson, USA) was collected and cultured for 5 days in an automated system. Positive samples were subcultured onto blood, chocolate and MacConkey media and reincubated. Endotracheal aspirates were first Gram stained to determine the number of polymorphonuclear leucocytes and epithelial cells per low power field. Results of Gram stain and microscopy were recorded as ≥ 25 or <25 polymorphonuclear cells per low powered field and > 10 or ≤ 10 epithelial cells per low powered field as appropriate. All samples were inoculated onto blood, chocolate and MacConkey agar for semi-quantitative culture. All resultant growth was reported. Identification of isolates from blood and ETA culture was done using routine microbiological methods including API and VITEK (bioMérieux, France). Antibiotic susceptibility was determined by disk diffusion or E-test according to CLSI guidelines and breakpoints [134].

For the purposes of analysis, when a diagnosis of VAP or other VARI was established, any cultured bacteria was treated as a pathogen if cultured at a concentration of 10^5 cfu/ml or above in ETA specimens [35]. In semiquantitative culture, bacterium with growth at level +++ or more was treated as pathogen.

2.2.6 Sample size

Based on a review of the available literature, the incidence of VAP among mechanically ventilated patients was estimated to be approximately 30%. A sample size of 600 patients enrolled was chosen as at this number an incidence of 30% with a 95% confidence interval of 3.7% could be detected.

2.2.7 Data management

All clinical information was recorded or placed in the patient's notes, in keeping with local practice. Relevant data were recorded onto a case record form (CRF) and checked for accuracy before single data entry onto an electronic database (CliRes, OUCRU, Vietnam). Internal checks of the entered data were performed to look for outliers and errors. Patients who spent less than 3 days on ventilators since enrolment or were treated with ECMO in the study period were excluded in the final analysis as the diagnostic definitions could not be applied to these two groups.

For the descriptive analyses of the endpoints proportions were used for categorical data and mean (standard deviation (SD), 95% confidence intervals (CI)) and/or median (inter quartile and full ranges) for continuous data supplemented by graphical displays where relevant. Comparative analysis was performed using Chi Square or Fisher's exact test for categorical data. For continuous data, the student's T test, Mann Whitney U test, and Wilcoxon rank sum test were used for normally distributed, skewed and paired data, respectively. Logistic regression was used to analysis risk factors. Two-sided P values <0.05 are considered significant. There has been no statistical adjustment for multiplicity testing, the implications of which are discussed where relevant.

2.2.8 Ethics

The conduct of this clinical study was consistent with the principles of the Declaration of Helsinki [135]. The study was approved by the Institutional Review Board of the National

Hospital for Tropical Diseases (reference 37/HDDD-NHTD) and Bach Mai Hospital in Hanoi, the Hospital for Tropical Diseases in Ho Chi Minh City and the Oxford University Tropical Research Ethics Committee (OxTREC, reference 153-12). Written informed consent was obtained from all patients or their legal representatives.

Chapter 3

Hospital Acquired Infections in Vietnamese Adult Intensive Care Units

3.1 Introduction

HAIs and AMR are growing public health problems of global importance [1, 136]. The prevalence of HAIs is substantially higher in LMICs than in high income countries, with an average prevalence of 15.5%, compared to a prevalence of 7.1% and 4.5% in Europe and USA, respectively [10]. HAIs are most common in ICUs, and it is here that they are often the result of infection with highly resistant bacteria requiring the use of extremely broad spectrum, expensive antibiotics. The HAI prevalence in ICUs ranges from 9.1% in the United States to around 23.0% in Europe and England [5, 7, 137-139], and even higher in LMICs with a pooled prevalence of 35.2% [1]. A recent report of the International Nosocomial Infection Control Consortium 2007-2012 from 503 ICUs shows that ventilator-associated pneumonia (VAP) is fifteen times and catheter-associated urinary tract infection four times higher in LMICs than in better resourced settings [45]. The ICU capacity in many LMICs has increased dramatically, in line with the rapid economic development in these countries. However there are often high occupancy rates, overcrowding, few isolation rooms, and inadequate resources for infection control all of which may contribute to the reported high incidence of HAIs and drug-resistant infections at ICU's in these settings [1, 140, 141].

Vietnam is one such LMIC that has had rapid economic growth and expansion of critical care services. Vietnam has a population of 91 million [142] and an increasingly sophisticated health care system, typical of countries in the region. Health expenditure per capita in Vietnam was around 100$ per annum in 2012, approximately a seventh of the regional average [142]. Prior to this study, there was no national surveillance system for HAIs in Vietnam and limited data about HAIs in ICUs. The few studies performed are small and only some included ICUs, but reported that the HAI prevalence in those ICUs ranged from 19.3%

to 31.3% [110, 112, 114-117]. Only one of these studies is from the international peer reviewed literature [110], the others are published in the Vietnamese medical literature [112, 114-117].

In order to provide up-to-date, systematic data and to demonstrate the feasibility of developing a national surveillance network for ICUs in a LMIC, we performed a prospective study on the prevalence and associated risk factors of HAI in ICUs across Vietnam [129].

3.2 Materials and Methods

Study design, hospital and patient selection

We conducted a repeated point prevalence survey (PPS) to determine the prevalence of HAIs, and to assess antimicrobial use and antimicrobial resistance using the methodology developed by the European Center for Disease Prevention and Control (ECDC) [14]. The survey was conducted on one day each month from October 2012 through September 2013 in 15 adult ICUs in 14 acute care hospitals, of which 6 were tertiary hospitals and 8 provincial hospitals, throughout Vietnam. Patients aged ≥ 18 years, admitted to participating ICUs before 8 a.m. on the survey day, and remaining there at the survey time were included regardless after that time patient was discharged or remain in that ICU. Data on outcome after the survey were not collected. More details of the methods are provided in chapter 2.

3.3 Results

3.3.1 Baseline data of participating hospitals

Hospital sizes ranged from 280 to 2362 beds (median 950; IQR 750-1650) and the participating ICU sizes ranged from 10 to 60 beds (median 20; IQR 18-31). Mean length of ICU stays per individual ICU ranged from 3.8 to 16.0 days with a median mean length of stay across the ICUs of 6.4 days (IQR: 4.8-9.3). At the time of the study there were no national antimicrobial therapy guidelines, but locally derived guidelines were used at 7 of 15 ICUs. In

each ICU one nurse took care of 1.9 to 5.9 beds (median 3.6, IQR: 3.1 - 4.4 beds) per 8-hour shift. During working hours, there was a median of 3.5 doctors (IQR: 2.5 - 4.8) for 10 ICU beds. Alcohol hand rub was available at the bedside in all participating ICUs. Median alcohol hand rub consumption per patient day was 66.4 ml (IQR: 23.7 - 100.5). More details concerning the hospitals and their participating ICUs are presented in Table A – 1 in Appendix A.

3.3.2 Patient characteristics

In total, 3,401 patients were screened, of whom 3287 (114 were excluded due to age < 18 years) were enrolled from 15 ICUs of 14 participating hospitals between October 2012 and September 2013. Data from the medical and surgical ICUs of H04 were collected separately but given their small size which are presented as one general ICU. More details of patient characteristics were presented in Table A – 2 in Appendix A. Due to prolonged ICU stay, 162 patients were enrolled in more than one survey leaving 3125 unique patients. There was a disproportionate number of patients from 2 ICUs (H10 (18%) and H09 (12%)), while most ICUs each contributed for 4 – 8% of the total patients. (Figure 3 – 1)

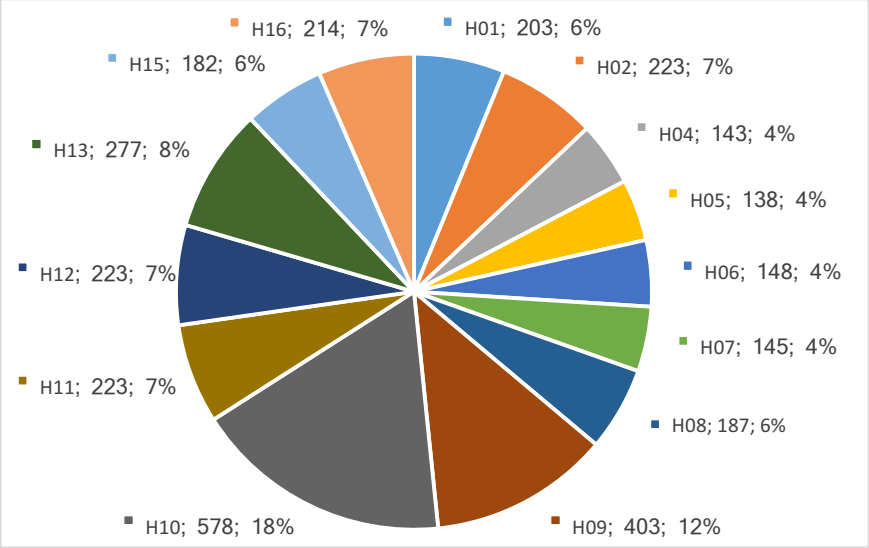


Figure 3 - 1. Proportion of total patients from each of the participating ICUs

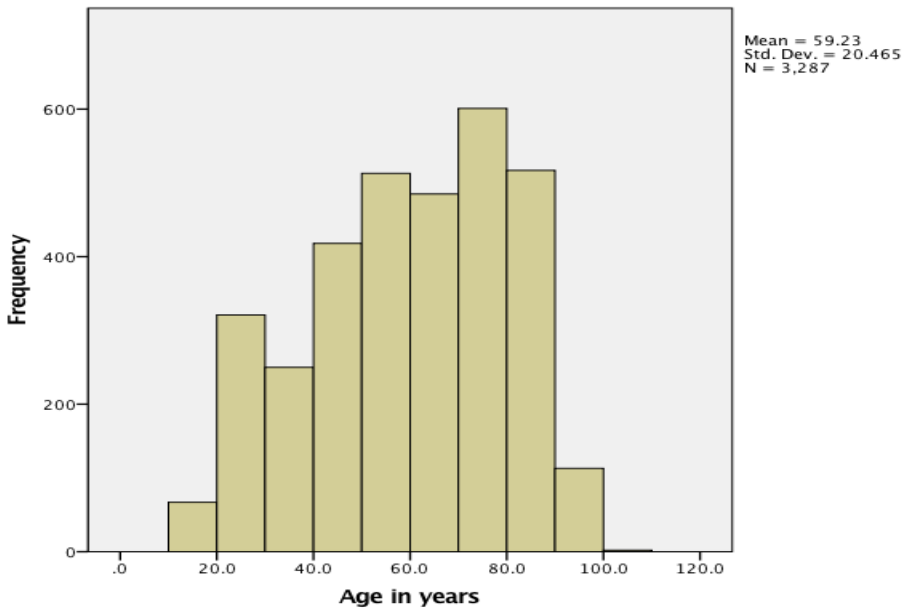


Figure 3 - 2. Age distribution of surveyed patients

The median age was 61.0 years (IQR 45.0-77.0, age distribution given in Figure 3 - 2) and 63.9% (2101/3287) of patients were male. Most patients (46.2%; 1427/3088; 199 missing) were admitted directly from the community, while 30.1 % (930/3088) of the patients entered the ICU from another department in the same hospital and 20.7% (638/3088) were referred from other hospitals, and others 3% (93/3088) were from community healthcare stations, long term healthcare facilities or private clinics. There was substantial heterogeneity between hospitals in the proportions admitted to ICU via different routes, with between 0 and 73% of patients in tertiary hospitals surveyed admitted from the community, whilst in the provincial hospital this ranged from 32% to 90%. (Figure 3 – 3)

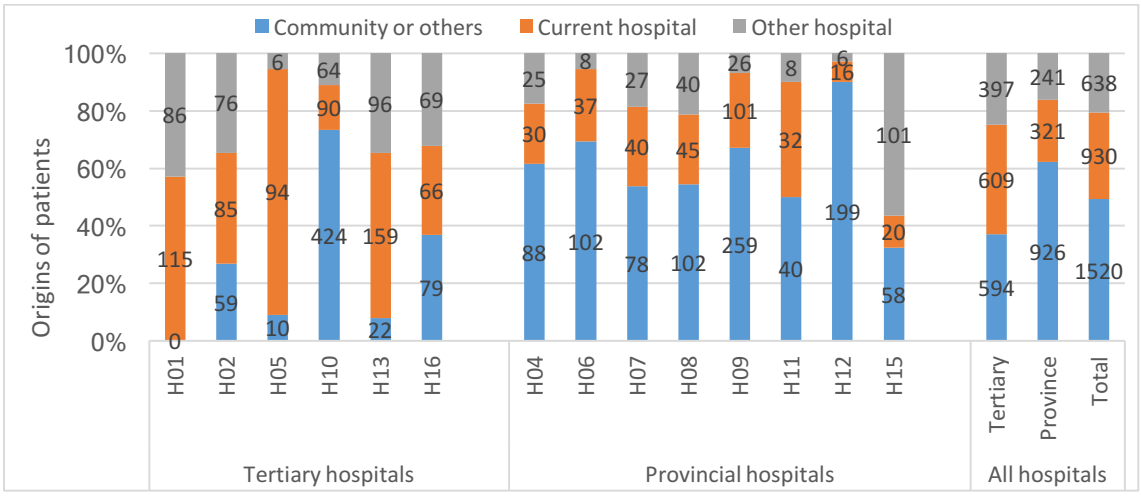


Figure 3 - 3. Location of surveyed patients before ICU admission

In general, infectious diseases were the most common reason for ICU admission with 46.3% (49.7% in provincial and 43.2% in tertiary ICUs), followed by other medical diseases (39.1%) and surgical diseases (14.6%). H01 and H15 were specialized hospitals on infectious diseases so almost all patients admitted to ICUs due to infectious diseases. H05 was specialized on surgery therefore nearly all patients admitted to ICU there due to surgical diseases. As with the route of admission to ICU, there was a great deal of heterogeneity in the cause of ICU admission across the ICUs surveyed. (Figure 3 - 4)

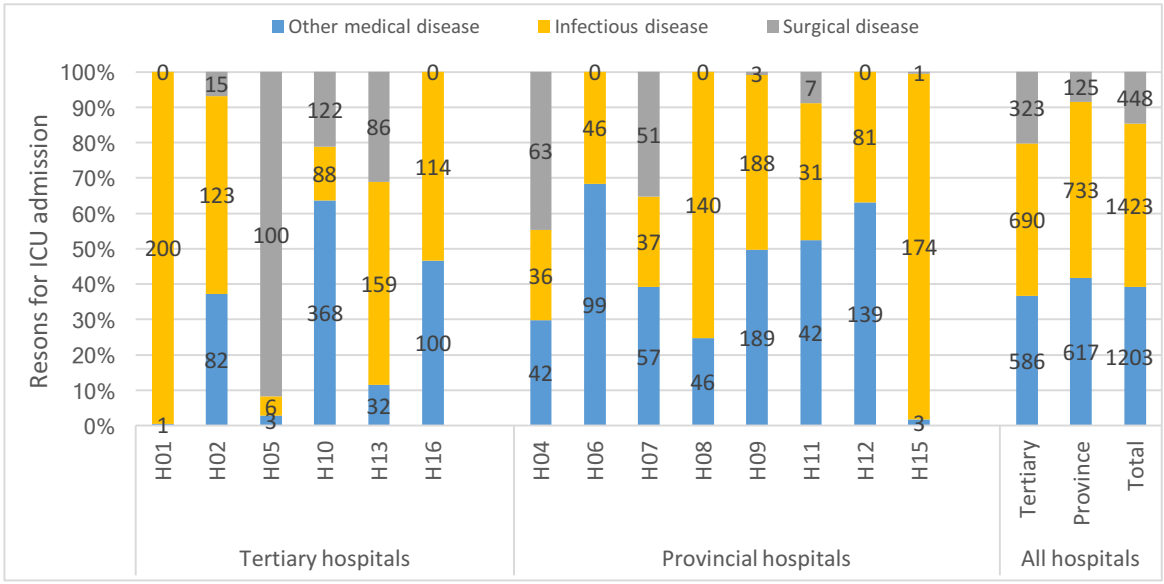


Figure 3 - 4. Reason for ICU admission amongst surveyed patients

Comorbidity was present in 39.6% of patients (1249/3151, 136 missing), of which 190 (15.2%) patients had two or more comorbidities. The most common comorbidities were: stroke sequelae 27.5% (343/1249), diabetes mellitus 24.8% (310/1249), chronic obstructive pulmonary disease 20.7% (259/1249), renal failure 11.5% (144/1249), harmful alcohol use 11.3% (141/1249), active malignancy 9.5% (119/1249), and induced immunosuppression 6.1% (76/1249). The proportion of patients with the lowest (5.8%) comorbidity was found in a surgical ICU (H05, surgical hospital), and in the other ICUs comorbidity ranged from 18.5% to 59.5% in tertiary ICUs and correspondingly 34.1% to 70.3% in provincial ICUs. (Figure 3 – 5)

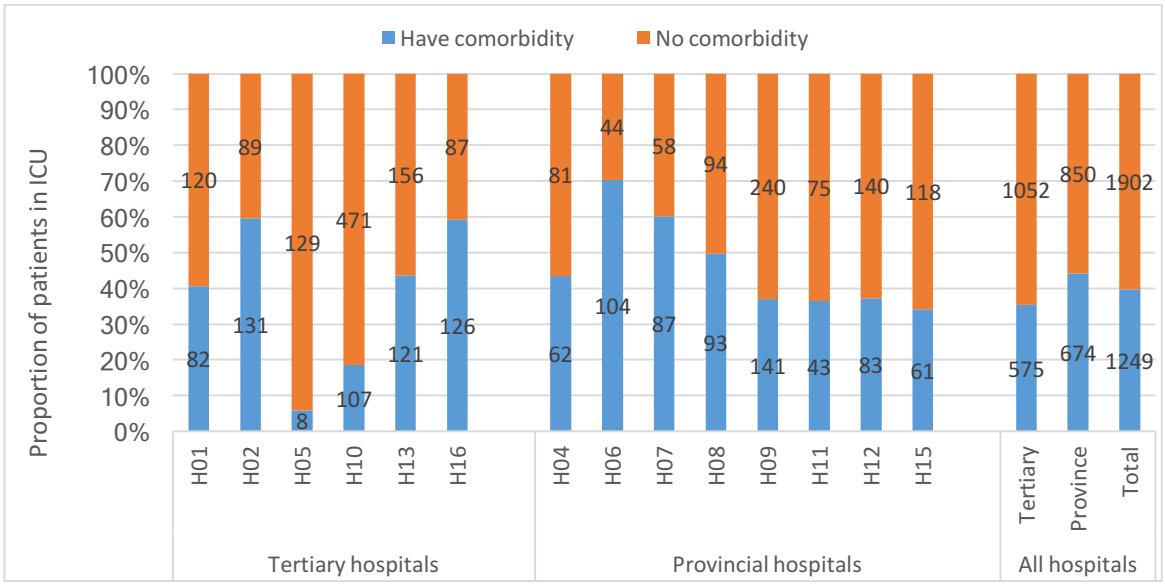


Figure 3 - 5. Proportion of surveyed patients with any comorbidity

Family members were involved in patient care in 63.0% (2072/3287) of patients, however family care was dependent upon the policies of each ICU and either did not occur in a unit (as it was not permitted) or occurred in close to 100% of cases in ICUs where it was permitted. (Figure 3 – 6)

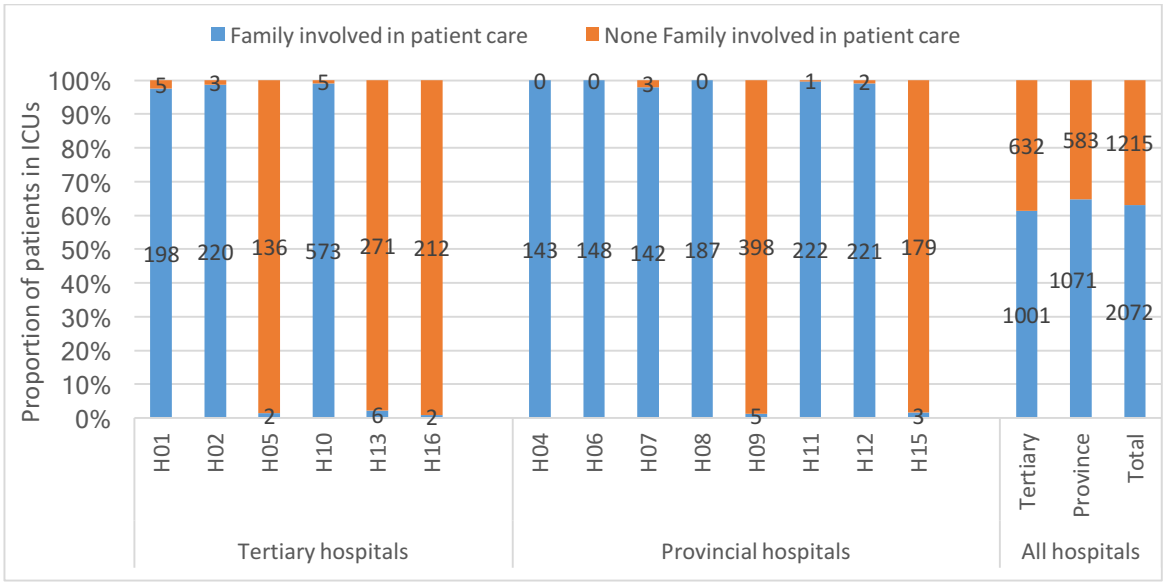


Figure 3 - 6. Proportion of surveyed patients with family member involved in patient care

Most patients in ICU of H05 experienced major surgery since admission while there was just one patient experienced surgery at ICU in H08. Overall, the proportion of patients that had

surgery after admission was 24.8%, and this proportion in tertiary ICUs (32.1%) was higher than in provincial ICUs (17.5%). (Figure 3 – 7)

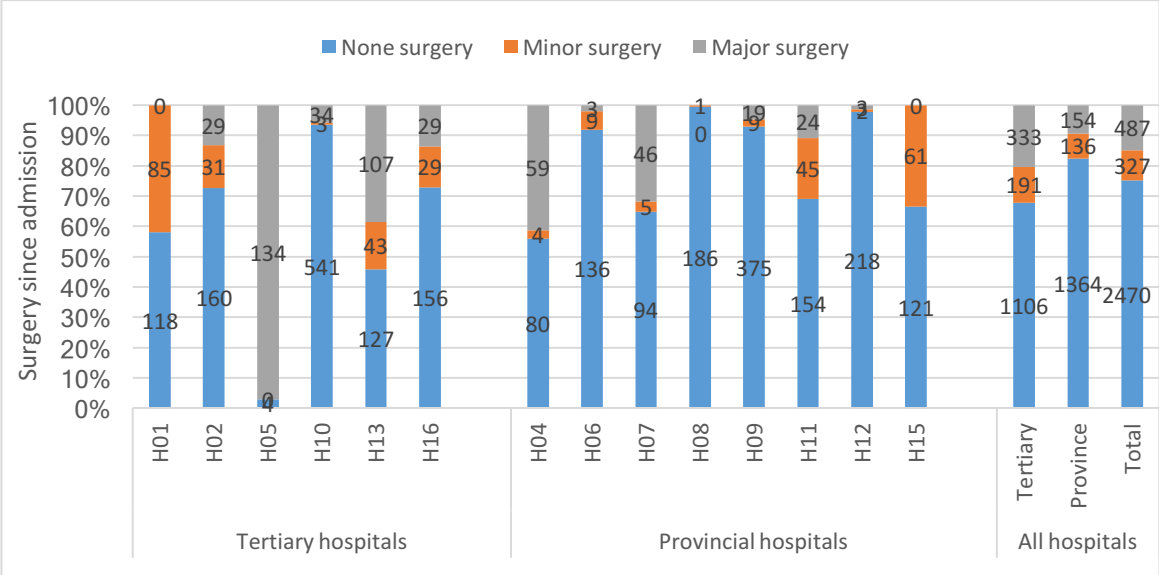


Figure 3 - 7. Proportion of surveyed patients that underwent surgery since admission

In total, 52.3% (1719/3287) of patients were intubated, with marked differences between the ICUs. This rate ranged from above 31.8% to 100% in tertiary ICUs and from 22.4% to 62.6% in provincial ICUs. The pooled proportion patients that were intubated was higher in tertiary ICUs than that in provincial ICUs. (Figure 3 – 8)

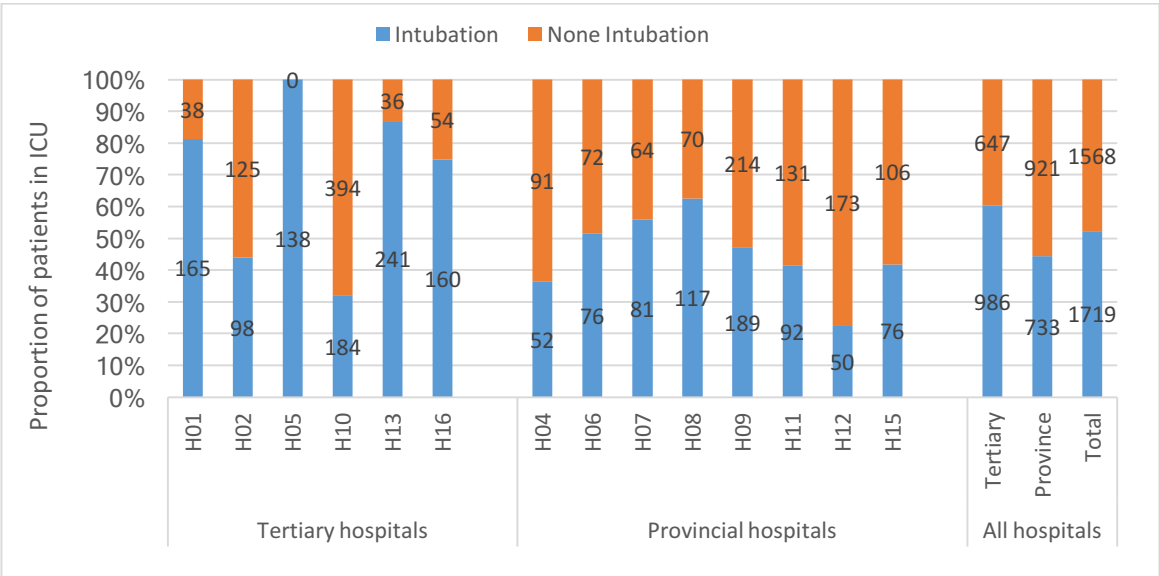


Figure 3 - 8. Proportion of surveyed patients intubated

The proportion of patients with a central vascular catheter was widely different between ICUs. The pooled proportion of patients with a central vascular catheter was 28.0% (921/3287) overall, 40% (654/1633) in tertiary ICUs (range from 8.5% to 96.4%), and 16.1% (267/1654) in provincial ICUs (range from 3.7% to 32.9%). Figure 3 – 9.

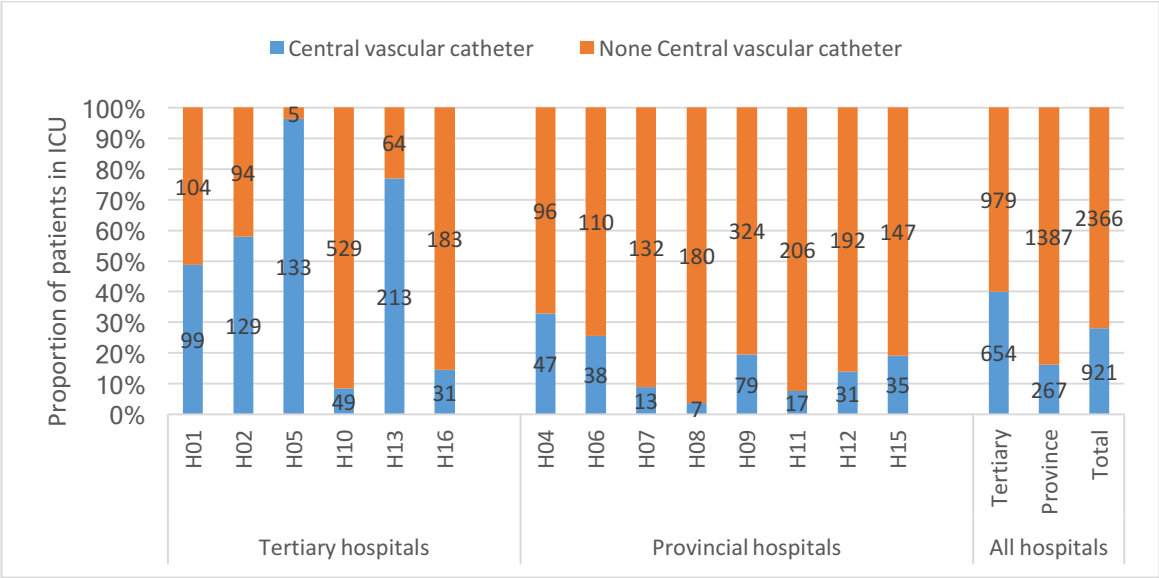


Figure 3 - 9. Proportion of surveyed patients with central vascular catheter

Patients with urinary catheter accounted for 49.2% (1616/3287) in total, 52.9% in tertiary ICUs (range 12.3% in H10 to 99.3% in H05), and 45.5% in provincial ICUs (range 17.6% in H08 to 65.8% in H09) (Figure 3 – 10). Only 8.2% of total patients experienced hemodialysis therapy on surveyed days. This rate ranged from 0% to 33.6% (Figure 3 - 11).

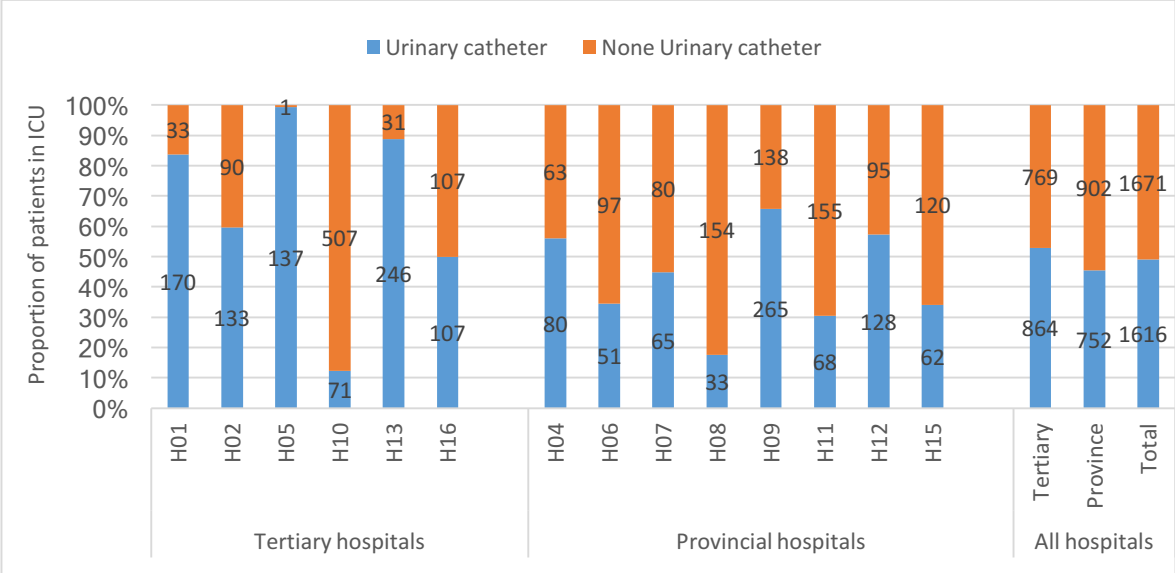


Figure 3 - 10. Proportion of surveyed patients with urinary catheter

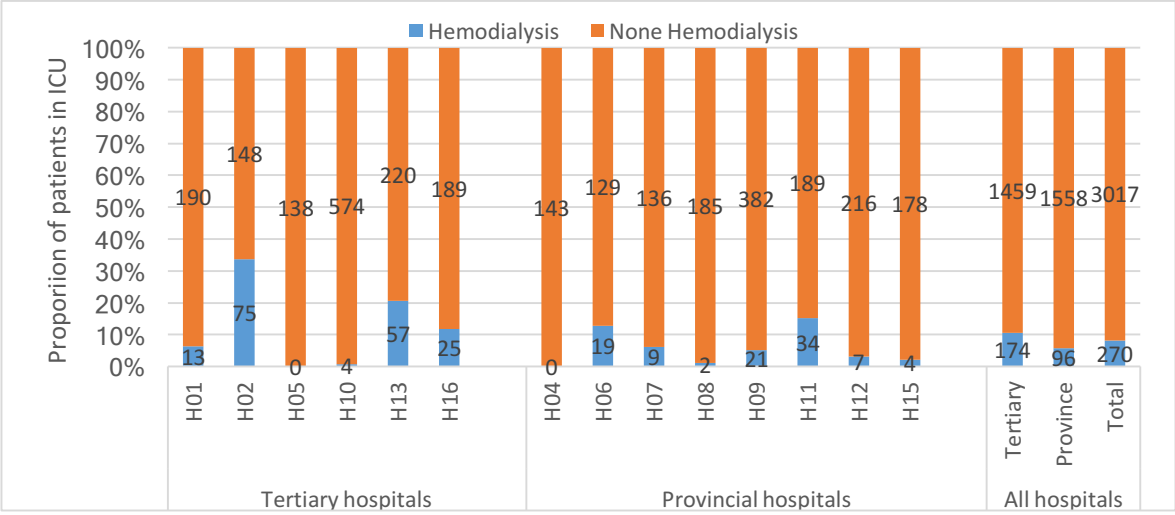


Figure 3 - 11. Proportion of surveyed patients having hemodialysis

3.3.3 HAI prevalence

Overall, 29.5% (965/3266 patients, 21 missing) had at least one HAI; 922 patients had one HAI, 39 patients had 2 HAIs, and 4 patients had 3 HAIs. The HAI prevalence ranged widely between ICUs from 5.6% to 60.9% with a median prevalence of 30.5%. Overall tertiary ICUs had higher HAI prevalence than provincial ICU, exception for H10, and hospital acquired pneumonia (HAP) was the most common HAI (79.4% [804/1012]), followed by blood stream infection (BSI) (4.4% [44/1012]), and surgical site infections (4.2% [42/1012]). For each ICU, HAP also was the most common HAI, its prevalence ranged from 19.7% to 58.0% patients in tertiary ICU with exception for H10 (4.0%) and from 9.8% to 34.3% patients in provincial ICUs (Table 3 – 1).

3.3.4 HAI origin and its relationship to a medical device

Most HAIs (84.5% [855/1012]) were acquired in the survey hospital: 42.5% (363/855) acquired prior to ICU admission and 57.5% (492/855) developed after ICU admission (Table 3 – 2). Among 705 first HAIs developed in the current hospital, the median time from hospital admission to onset of HAI was 7 days (IQR: 3-15 days). HAIs developing within 30 days from hospital admission accounted for 92.6% (653/705) of all first HAIs and the median time from hospital admission to onset HAI was 7 days (IQR: 3 – 12 days) (details was

presented in figure 3 – 12). Device-associated HAIs accounted for 643/1012 (63.5%) of HAIs, mainly VAP (589/643 [91.6% of device-associated HAIs]) (Table 3 - 2).

Table 3 – 1. Proportion of HAI types in each ICU

ICU at Hospital	Pneumonia	Blood stream infection	Surgical site infection	Gastro - intestinal infection	Urinary tract infection	Central nervous system infection	Skin & soft tissue infection	Other infections	Total HAIs	Total patients with HAI
H01, n (%)	40 (19.7)	3 (1.5)	20 (9.9)	0	2 (1.0)	6 (3.0)	0	0	71 (35.0)	68 (33.5)
H02, n (%)	60 (27.5)	4 (1.8)	4 (1.8)	8 (3.7)	2 (0.9)	4 (1.8)	2 (0.9)	3 (1.4)	87 (39.9)	84 (38.5)
H05, n (%)	80 (58.0)	2 (1.4)	2 (1.4)	0	0	0	0	0	84 (60.9)	84 (60.9)
H10, n (%)	23 (4.0)	0	3 (0.5)	2 (0.3)	0	4 (0.7)	7 (1.2)	1 (0.2)	40 (6.9)	40 (6.9)
H13, n (%)	110 (39.7)	8 (2.9)	8 (2.9)	20 (7.2)	9 (3.2)	1 (0.4)	1 (0.4)	2 (0.7)	159 (57.4)	144 (50.5)
H16, n (%)	118 (55.4)	4 (1.9)	0	5 (2.3)	3 (1.4)	0	2 (0.9)	0	132 (62.0)	126 (59.2)
H04, n (%)	14 (9.8)	0	0	0	2 (1.4)	0	0	0	16 (11.2)	15 (10.5)
H06, n (%)	36 (25.5)	7 (5.0)	0	1 (0.7)	1 (0.7)	0	0	0	45 (31.9)	43 (30.5)
H07, n (%)	21 (14.5)	0	0	0	0	0	0	0	21 (14.5)	21 (14.5)
H08, n (%)	39 (20.9)	1 (0.5)	0	0	0	0	0	0	40 (21.4)	40 (21.4)
H09, n (%)	136 (34.3)	0	3 (0.8)	2 (0.5)	1 (0.3)	2 (0.5)	1 (0.3)	2 (0.5)	147 (37.0)	146 (36.8)
H11, n (%)	75 (33.8)	0	2 (0.9)	1 (0.5)	2 (0.9)	2 (0.9)	2 (0.9)	4 (1.8)	88 (39.6)	81 (36.5)
H12, n (%)	28 (12.6)	4 (1.8)	0	0	0	0	0	4 (1.8)	36 (16.1)	36 (16.1)
H15, n (%)	24 (13.3)	11 (6.1)	0	1 (0.6)	7 (3.9)	0	0	3 (1.7)	46 (25.4)	41 (22.7)

Hospitals in the first block of rows (H01, H02, …, H16) are tertiary hospitals, and in the second block of rows (H04, H06, …, H15) are provincial hospitals

Table 3 - 2. Location HAI was acquired and association with medical devices.

Type of infections	**Location Acquired HAI**				**Related device**			**Total No. of HAI, n (%)**
	Current hospital		**Other hospital**	**UNK**	**Yes**	**No**	**UNK**	
	In ICU	**Out ICU**						
Pneumonia & LRTI[a], n (%)	389 (48.4)	301 (37.4)	60 (7.5)	54 (6.7)	589 (73.3)	120 (14.9)	95 (11.8)	804 (79.4)
Bloodstream infection, n (%)	34 (77.3)	8 (18.2)	2 (4.5)	0	27 (61.4)	11 (25.0)	6 (13.6)	44 (4.4)
Surgical site infection, n (%)	23 (54.8)	11 (26.2)	6 (14.3)	2 (4.8)	NA	NA	NA	42 (4.2)
Gastrointestinal infection, n (%)	13 (32.5)	19 (47.5)	7 (17.5)	1 (2.5)	NA	NA	NA	40 (4.0)
Urinary tract infection, n (%)	18 (62.1)	8 (27.6)	3 (10.3)	0	27 (93.1)	2 (6.9)	0	29 (2.9)
Central nervous system infection, n (%)	5 (26.3)	4 (21.1)	8 (42.1)	2 (10.5)	NA	NA	NA	19 (1.9)
Skin and soft tissue infection, n (%)	2 (13.3)	6 (40.0)	1 (6.7)	6 (40.0)	NA	NA	NA	15 (1.5)
Other infections[b], n (%)	8 (42.1)	6 (31.6)	2 (10.5)	3 (15.8)	NA	NA	NA	19 (1.9)
Total, n (%)	492 (48.6)	363 (35.9)	89 (8.8)	68 (6.7)	643 (73.3)	133 (15.2)	101 (11.5)	1012 (100)

UNK: unknown or missing data; NA: Not applicable; LRTI: low respiratory tract infection

[a] Only one case of LRTI

[b] Including: nine cases of systemic infection, four catheter related infections, four reproductive tract infections, one endocarditis and one eyes ear nose throats infection not classified.

Note: Twenty-one patients whose infection could not be differentiated between community-acquired and hospital-acquired infection were excluded from calculating HAI prevalence.

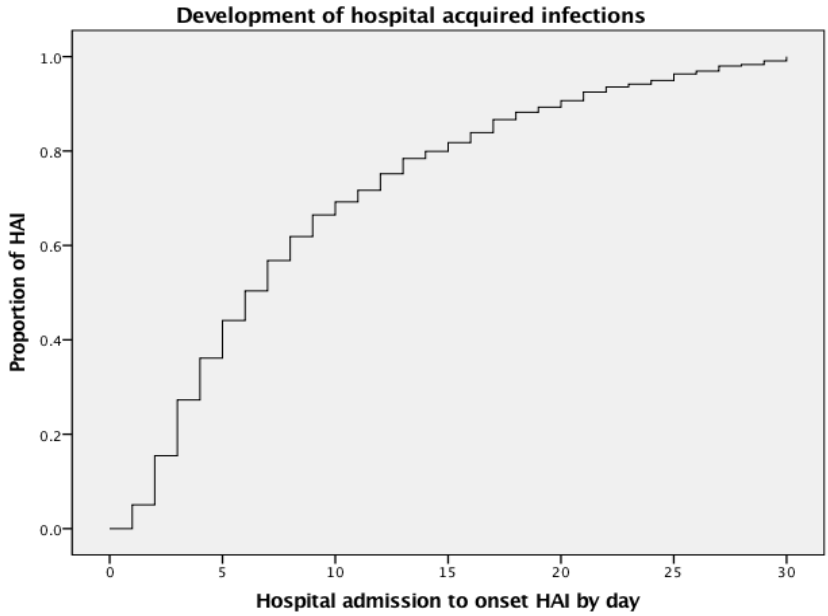


Figure 3 – 12. Time to development of HAI in current (surveyed) hospital over 30 days

3.3.5 Risk factors for HAIs Acquired in ICU

We assessed risk factors for ICU-acquired HAIs in 2,618 patients who were enrolled in the study for the first time and had no HAI at ICU admission. The prevalence of HAI among these patients at survey time was 16.2% (424/2618 patients). In a univariate analysis numerous factors were statistically associated with HAI. The highest risk factors associated with HAI were intubation (odds ratio [OR] 6.31 [95% CI 4.86-8.18]), having surgery after hospital admission (minor surgery OR 4.78 [95% CI 3.57-6.40], major surgery OR 3.78 [95% CI 2.90-4.93]), and urinary catheterization (OR 3.90 [95% CI 3.09-4.92]). (Table 3 - 3).

Table 3 - 3. Risk factors for developing HAI in ICU

Risk factors	No. of patients (total = 2618), n	Patients with HAI (total = 424), n (%)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	P value	OR (95% CI)	P value
Gender						
Male	1656	271 (16.4)	*1.03 (0.83-1.28)*	0.758	1.29 (0.98-1.69)	0.072
Female	962	153 (15.9)	*Reference*		*Reference*	
Missing	0				141	
Age group						
18 – 60 years	1344	202 (15.0)	*Reference*		*Reference*	
> 60 years	1274	222 (17.4)	*1.19 (0.97-1.47)*	0.097	1.13 (0.86-1.48)	0.392
Missing	0				141	

Risk factors	No. of patients (total = 2618), n	Patients with HAI (total = 424), n (%)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	P value	OR (95% CI)	P value
Location of patients at admission to ICU						
Community and others	1352	144 (10.7)	*Reference*		*Reference*	
Same hospital	655	171 (26.1)	*2.96 (2.32-3.79)*	< 0.001	1.40 (0.97-2.00)	0.068
Other hospital	507	109 (21.5)	*2.30 (1.75-3.02)*	< 0.001	1.25 (0.85-1.83)	0.262
Missing	104				141	
Reason for admission						
Medical disease	1029	120 (11.7)	*Reference*		*Reference*	
Infectious disease	1106	214 (19.3)	*1.82 (1.43-2.31)*	< 0.001	0.99 (0.71-1.38)	0.942
Surgery	368	90 (24.5)	*2.45 (1.81-3.32)*	< 0.001	1.05 (0.59-1.87)	0.876
Missing	115				141	
Comorbidity						
No comorbidity	1560	250 (16.0)	*Reference*		*Reference*	
Have comorbidity	972	171 (17.6)	*1.12 (0.90-1.38)*	0.303	0.72 (0.54-0.95)	0.021
Missing	86				141	
Surgery after admission						
None surgery	2009	219 (10.9)	*Reference*		*Reference*	
Minor surgery	252	93 (36.9)	*4.78 (3.57-6.40)*	< 0.001	1.74 (1.15-2.63)	0.009
Major surgery	354	112 (31.6)	*3.78 (2.90-4.93)*	< 0.001	1.18 (0.72-1.96)	0.510
Missing	3				141	
Intubation						
Yes	1252	346 (27.6)	*6.31 (4.86-8.18)*	< 0.001	2.52 (1.81-3.51)	< 0.001
No	1366	78 (5.7)	*Reference*		*Reference*	
Missing	0				141	
Central vascular catheter						
Yes	693	197 (28.4)	*2.97 (2.39-3.68)*	< 0.001	1.75 (1.20-2.55)	0.004
No	1925	227 (11.8)	*Reference*		*Reference*	
Missing	0				141	
Urinary catheter						
Yes	1226	312 (25.4)	*3.90 (3.09-4.92)*	< 0.001	2.03 (1.45-2.84)	< 0.001
No	1392	112 (8.0)	*Reference*		*Reference*	
Missing	0				141	
Hemodialysis						
Yes	203	51 (25.1)	*1.84 (1.31-2.57)*	< 0.001	0.99 (0.62-1.59)	0.981
No	2415	373 (15.4)	*Reference*		*Reference*	
Missing	0				141	
Peripheral vascular catheter						
Yes	2202	321 (14.6)	*0.52 (0.40-0.67)*	< 0.001	1.89 (1.23-2.90)	0.004
No	416	103 (24.8)	*Reference*		*Reference*	
Missing	0				141	
Family involved patient care						
Yes	1717	190 (11.1)	*Reference*		*Reference*	
No	901	234 (26.0)	*2.82 (2.28-3.48)*	< 0.001	0.60 (0.19-1.85)	0.373
Missing	0				141	
Each day longer from ICU admission to survey time						
In analysis	2513	424 (16.9)	1.08 (1.07-1.10)	< 0.001	1.11 (1.09-1.12)	< 0.001
Missing	105				141	

In multivariate logistic regression, all risk factors were included and adjusted for hospital sites. Seven risk factors independently associated with HAIs, which included: intubation (OR 2.52 [95% CI 1.81 - 3.51]), urinary catheter (OR 2.03 [95% CI 1.45 - 2.84]), minor surgery after admission (OR 1.74 [95% CI 1.15 - 2.63]), central vascular catheter (OR 1.75 [95% CI 1.20 - 2.55]), peripheral vascular catheter showed a protective effect in univariate analysis but was associated with a significant increased risk for HAIs in multivariate analysis (OR 1.89 [95% CI 1.23 - 2.90]), and every one day longer of ICU stay (OR 1.11 [95% CI 1.09 - 1.12]), having comorbidity showed higher risk in univariate analysis but turn out to have some protection from HAI in multivariate analysis (Table 3 - 3).

3.4 Discussion

To date, this is the largest study on HAIs in ICUs in Vietnamese hospitals. The HAI prevalence in this study (29.5%, 965/3266 patients) was lower than the pooled HAI prevalence of 35.2% reported from other LMICs ICUs. But the individual hospital prevalences vary widely, from 6.9% to 60.9% in our study and from 4.4% to 88.9% in other LMICs [1]. This reflects the heterogeneity amongst ICUs, so comparing pooled prevalences need to be interpreted carefully. However, the high prevalence of HAI in our study, particularly at three of the ICUs (H05, H13, H16), is concerning and suggest further investigations and actions to prevent infections are required.

The HAI prevalence in the current study is higher than that reported from adult ICUs in European hospitals using almost the same protocol (23.0%, 1750/7613 patients) [5] and in ICUs in Southern Europe, Turkey and Iran (23.5%, 176/749 patients) [138] and much higher than rate of 9.1% (156/1707) in ICUs in the United States in 2011[7]. In a period of surveillance in European ICUs in 2007, ICU-acquired infection was 7.0% for pneumonia, 3.9% for BSI, and 6.8% for UTI amongst patients who stayed longer than 2 days in ICU. In our study, total HAP, BSI, and UTI were 23.4%, 1.3%, and 1.2% respectively.

Our study showed a point prevalence of 16.2% for infections acquired in the ICU and there were numerous risk factors for infection. Medical device use was high in the ICUs, ranging from 29.3 to 73.3 days per 100 patient days for intubation, 56.2 to 87.9 days for central vascular catheter, and 65.8 to 89.6 days for urinary catheter [40]. Furthermore, there were few single rooms in the surveyed ICUs and common rooms usually contained 4 – 5 beds, ranging up to 30 beds (Table A – 1 in Appendix A). The recommendation from the European Society of Intensive Care Medicine is that number of isolation rooms per total ICU beds should range from 1-2 rooms per 10 ICU beds and may be up to 5 – 6 rooms per 10 ICU beds in some special ICUs (burnt units, infection units, transplantation units, etc.) [143]. In addition, low nursing staff : patient ratios (0.81 – 2.5) [142] and high bed occupancy rates [108], often over 110%, will have contributed to the high prevalence of HAIs acquired in the ICU [143]. These conditions make successful infection control very challenging. In particular, the lack of nursing staff for patient care allows little time for proper infection control measures [144-146]. This is supported by the smaller amount of alcohol hand rub used compared to ICUs in wealthier settings: a median of 66.4 ml (IQR: 23.7–100.5 ml)/patient day (Table A – 1 Appendix A), compared with a median of 83 ml (IQR: 64–105)/patient day in ICUs of Germany in 2010 [147].

In short, effective implementation of infection control programmes to limit and control HAIs requires good knowledge and skills, but also requires good basic ICU infrastructure and enough staff to achieve strict compliance with infection control measures. These problems are a major challenge for LMICs, but it need to be addressed urgently due to huge burden of HAIs on public health and economics [1, 6, 62, 63, 148].

Hospital-acquired pneumonia (HAP) was the most common type of HAI, as reported in other studies [1, 10, 138]. HAP accounted for 23.4% of total surveyed patients and 79.4% of all HAIs in our study, nearly double that reported (40.0% - 45.3%) in ICUs of developed countries [5, 137]. A large proportion of HAP (37.4%, 301/804), and also of total HAIs

(35.9%), were acquired in the same hospital before admission to ICU and was the cause of the ICU admission. In addition to high proportion of device related HAIs (Table 3 - 2), this figure raises the need for an effective infection control program outside ICU, particularly in emergency departments where invasive devices were commonly done for HAI prevention.

Blood stream infections (BSI) accounted for 4.4% of all HAI, considerable lower than the reported about 18.0% in European ICUs [5]. That survey did not show the proportion of patients in ICUs with invasive device. However, in another study in European ICUs in 2007, BSI rate was 3.9% of all patients that stayed more than 2 days in ICU and with utility of central vascular catheter of 56.2 to 87.9 days per 100 patient days [40]. In our study, the proportion of patients with a central vascular catheter was 28.0%. Therefore, the lower rate of BSI in our study may have been due to the lower proportion of patients with central vascular catheter and the high HAP prevalence. There might, however, have been an underestimation of BSI due to underutilization of blood cultures. Only 243 blood cultures were taken from the 3287 patients in the 24 hours preceding the survey day, which is lower than anticipated although we are not aware of any comparable data from other settings.

Multivariate analysis identified intubation as an important risk factor, which combined with the high prevalence of HAP suggests that future interventions should target this risk factor. Potential interventions to assess include ventilation and sedation strategies, cuff and tracheal tube design, cuff pressure management [149]. Strategies like selective gut decontamination using polymyxins may not be appropriate in this setting with high antimicrobial resistance background rates with colistin as last resort drug [150] and poorly resourced infection control to contain any potential colistin resistance generated by the technique. Univariate analysis showed that the involvement of the patient's family in patient care was a protective factor from HAI but in multivariate analysis this factor turned to associate with higher risk for HAI although it did not reach statistically significant. As ICUs had department-wide policies to either allow or forbid family from taking care of their admitted family member this practice

was highly clustered at the ICU level, the result needs to be interpreted with caution. Further research is needed to understand the risks for HAI regarding family members involved in patient care. The caution also need for comorbidity assessment. This factor is usually associated with higher risk for HAI but in this study it was associated with lower risk for HAI in multivariate analysis. This could be the heterogeneity of comorbidity which included ten kinds of comorbidities and within the causes of admission.

National surveillance systems for HAI are scarce in LMIC settings yet ongoing surveillance is crucial to informing policymakers of the needs of the population and high quality data is critical to the development of potential interventions applicable at the national level. In our study, we did not found statistically different risk for HAI between male and female gender, between age > 60 years and age 18 – 60 years, patients referenced from other hospitals and patients came from community, patients admitted to ICU due to infection or surgery and patients admitted to ICU due to medical disease, patients with and without comorbidity. A survey of all departments in European acute hospitals found that male gender, older age, and surgery since admission were associated with higher risk for HAI [5]. However, another study on HAI in ICUs in Europe did not find a statistically significant difference in risk for HAI between patients admitted to ICUs due to medical and surgical reasons [40]. A survey in all departments in acute hospitals the United States in 2010 found that older age was associated with higher risk for HAI [7]. These reported differences could be due to differences in study populations. Our study was only conducted in ICU, while other studies involved patients in all departments in acute hospitals. Another factor that may explain the differences was that most HAIs in our study (86.7%) were device-related, whilst this proportion in the studies in Europe and the United States were 45.9% and 25.6%, respectively [5, 7].

As other studies have reported [5, 7], our study found that each additional day in ICU and the presence of any medical device was associated with statistically significant higher risk for HAI. Therefore, one way to reduce HAI prevalence is to reduce the duration of ICU stays and

improve the use of medical devices. In particular, medical device related infections may be reduced by assiduous hand hygiene, improved techniques and expertise in applying the device, and removing the device as early as possible.

Study limitations

As HAIs had not previously been routinely surveyed in Vietnamese hospitals, criteria for the diagnosis of specific HAI may not have been fully understood, potentially leading to misclassification of specific HAIs. To limit this problem, we organized several workshops and site visits to train doctors. The enrolment of patients who were just admitted to ICU before 8.00 A.M. then were discharged from ICU soon after survey time could lead to underestimate the HAI prevalence. However, the mean ICU stays at participating ICUs ranged from 3.8 to 16 days (Table A – 1 in Appendix A) which means that number of these cases was not many and its impact on the HAI prevalence was probably not significant. HAIs also are a sensitive issue in Vietnam; therefore, ICU doctors may not have reported all HAIs, leading to an underestimation. To minimize this effect data, hospitals were anonymized using codes. When data were uploaded we ran data checks and returned queries to doctors that needed to be resolved. We therefore think that the hands-on supervision and input from the study team ensured that data quality was optimal.

Conclusions

There is a high prevalence of HAIs in Vietnamese ICUs with more than one third acquired before ICU admission and a predominance of hospital acquired pneumonia. This needs to be urgently addressed by strengthening in infection control efforts for not only ICUs but the other departments of hospitals. Besides these, solutions to shorten length of stay in ICU and limit use of invasive device are important to limit HAI in ICUs. These interventions should be systematically implication at national and local level.

Chapter 4

Antibiotic Use and Resistance in Vietnamese Adult Intensive Care Units

4.1 Introduction

Antibiotic resistance results in bacteria being able to grow in the presence of antibiotics to which it used to be susceptible [151]. Antibiotic resistance is a global public health problem as it increases hospital stay, morbidity, mortality, and health expenditure. It is estimated that in the European Union annually antibiotic resistance leads to 25,000 deaths annually, an additional 2.5 million hospital days, at a cost of 1.5 billion Euros [152]. In the United States of America (with about 300 million citizens) antibiotic resistance results in more than 2.0 million illnesses with more than 23,000 deaths, and overall direct societal costs of 20 billion US$ [153]. In Thailand (population 70 million), antibiotic resistance leads to over 3,2 million additional hospital days and more than 38,000 deaths, costing up to 200 million US$ directly per year [154].

A systematic review by WHO in 2014 illustrates that the mortality in patients with antibiotic resistant infections is double to that in patients with susceptible infections [155]. The World Economic Forum has estimated that antibiotic resistance can decrease GDP by 0.4% to 1.6% [148]. A report by Jim O' Neil states that if no effective actions on the present situation of antimicrobial resistance are taken, there would be 10 million deaths and a decrease of globally GDP 2 – 3.5% (100 trillion US$) worldwide every year. [156].

Intensive care units (ICUs) are hotpots for antimicrobial resistance, due to abundance of risk factors for hospital acquired infections in combination with a high level of antibiotic use, a key driver of rising antibiotic resistance levels. In high income countries, the proportion of ICU patients prescribed antibiotics is higher than in other wards. A survey by ECDC in 947 European acute care hospitals of 30 European nations in 2011 – 2012 showed that 56.5% patients in ICUs was used antimicrobials on survey day compared with that of about 41% in

surgical wards and 37% in medical wards [5]. A survey in the USA in 2011 with 183 hospitals and 5860 surveyed patients showed that prevalence of antimicrobial use in ICUs was 57.7% while in the other wards was 48.6% [98]. Another survey in 37 Australian and New Zealand ICUs in 2007 showed that 71% ICU patients was on antimicrobial use on the surveyed days [99]. In a German study of 40 ICUs, median antibiotic use was 135.1 DDD/100 patient days (ranging from 42.7 to 279.8) in whole period 2001 to 2004 with an increasing trend from 124.7 DDD/100 PD in 2001 to 138.5 DDD/100 PD in 2004 but median carbapenem use was not changed, 6.65 DDD/100 PD in 2001 and 6.57 DDD/100 PD in 2004 with *P. aeruginosa* resistant to carbapenem from 1.71 isolates/1000 PD in period 2001- 2003 and 1.65 isolates/1000 PD in 2004 [96]. A retrospective observational study on 2422 patients at a 12 beds surgical ICU in German from 2010 to 2012 with introduction of an antimicrobial stewardship programme combination with procalcitonin guideline for antibiotics discontinuation in 2011 showed a decreased antibiotic use from 100.5 DDD/100 PD in 2010 to around 79.19 DDD/100 PD in 2012 with a decrease antibiotics cost in the ICU from 54498 EUR to 33297 EUR (from 16.30 EUR/PD in 2010 to 9.26 EUR/PD in 2012) and no significant change in mortality and ICU stay, 10.4% vs 11.4% and median (IQR) of 1 (1 – 3) days vs 1 (1 - 4) days for 2010 vs 2012 respectively [97].

There is little data on antibiotic use and resistance in Vietnam. A survey at 15 hospitals across Vietnam in 2008, mean antibiotics consumption was 274.7 DDD/100 patient days [157]. Thus, whilst it is not without risk to draw comparisons between studies of different design, it appears that the Vietnamese hospitals as a whole were prescribing more antibiotics than the intensive care units in Germany. A situational analysis published in 2010 and funded by GARP, showed antibiotics consumption in Vietnamese hospitals accounted for 36% of whole hospital treatment expenditure [158]. This high antibiotic consumption obviously was a main factor causing high levels of antibiotic resistance in Vietnam. Rapid increase in antibiotics resistance could be conceived through the rate of *Streptococcus pneumoniae* isolated from blood and cerebral spiral fluid of meningitis patients in Ho Chi Minh City resistant to

penicillin which increased from 8% to 56% in a short time from 1993 - 1995 period to 1999 – 2002 period [159]. In 2001, another survey showed that *Streptococcus pneumoniae* resistant to penicillin was highest in Vietnam (71.4%) compared with average 52.4% for 11 surveyed Asian countries (including Vietnam) [160]. Recently, a multicenter study on pathogens of BSI, nosocomial pneumonia, and complicated intra-abdominal infections in Asia – Pacific in 2010 also found that overall carbapenem resistance was highest in Vietnam 35.0% compared with 23.0% in common, of which carbapenem resistance among *A. baumannii, P. aeruginosa*, and Enterobacteriaceae were 89.5%, 46.7%, and 5.6% compared with 73.0%, 29.8%, and 2.8% respectively of overall five countries [161]. That study also indicated that prevalence of extended spectrum beta – lactamase among Enterobacteriaceae isolated in ICUs also highest in Vietnam with 81.0% while the second was 58.8%, and overall was 43.8%.

There was limited data available on antibiotic resistance and antibiotic use in Vietnamese ICUs. A study on pathogens of HAI at ICU, Emergency Department (ED), and Centre for Toxicology Control of Bach Mai hospital in 2003 showed that most common isolates were *A. baumannii* 27.3% (44/161) and *P. aeruginosa* 27.3% (44/162) with rate of carbapenem resistance was 13.6% (6/44) and 18.2% (8/44) respectively [162]. This study also found that *K. pneumoniae* and *E. coli* accounted for 9.9% (16/161) and 6.8% (11/161) of isolates from HAI, respectively, with no strain resistant to carbapenems. A study on pathogens of hospital acquired pneumonia at ICU of Bach Mai hospital in 2008 – 2009 found that most common bacteria isolated was *A. baumannii* 44.7% (59/132) and *P. aeruginosa* 17.4% (23/132) with carbapenem resistance was 90.7% (49/54), and 68.4% (13/19), respectively [119]. About antibiotic use in ICU, a survey at Bach Mai Hospital in 2006 found that antibiotics use in total patient at ICU, ED, and Centre for Toxicology Control was 54.3% (25/46) while in Obstetrics and Surgical Departments was the highest at 97.8% (45/46) and 95% (113/119) respectively; and lowest at internal departments at 40.3% (441/1094) [112]. A survey at three provincial hospitals, one district hospital, and one centre for dialysis in Hanoi city in 2006 found that proportion of patients on antibiotic use was 90.3% (56/62) at ICUs, highest up to 95.3%

(143/150) at pediatrics departments and lowest at internal department 60.1% (333/554) [114]. A survey at three provincial hospital in the North in 2005 showed that proportion of patients on antibiotic use was 61.0% (25/41) at ICUs while in surgical departments was 64.4% (76/118) and highest at obstetric departments of 81.6% (71/87) [115].

Despite this disturbing picture of very high levels of resistance in the region, only limited data available on antibiotic use and resistance in ICUs specially, in Vietnam. These data also showed high levels of carbapenems resistance in HAI pathogens and proportion of patients on antibiotic use. However, there was almost no data on antibiotic consumption in Vietnamese ICUs. The magnitude of antibiotic use and resistance in ICUs in Vietnam is needed to inform policies and interventions. This chapter aims to describe antibiotic use and antibiotic resistance in ICUs of 14 hospitals across Vietnam.

4.2 Material and Methods

A point prevalence survey (PPS) on hospital acquired infections (HAIs) and antimicrobial use was done monthly on a single day at ICUs of 14 participating hospitals across Vietnam from October 2012 to September 2013. The hospitals included 6 tertiary and 8 provincial hospitals. The design of the PPS is based on the methodology developed and used by the European Center of Diseases Prevention and Control (ECDC) [14]. Antimicrobial use is expressed in days of therapy (DOT) [130, 163]. One DOT represents the use of a single antimicrobial agent on a given day regardless of the dosage, which is normalized to DOT/100 patient-days (PD). If one patient received two antimicrobial agents at a given day means that the patient used 2 DOT/PD or 200 DOT/100 PD. Antimicrobial consumption measured by DDD is different to DOTs [130]. Both metrics are used to measure antimicrobial consumption. DDD is used to measure exactly amount of antimicrobial consumption according to WHO standards, and DOT is used to evaluate relatively antimicrobial consumption and reflects better clinical practice. More details in methods are presented in chapter 2.

4.3 Results

A total of 3287 patients (equal to 3287 patient days) were included in the final analysis with the median age of 61.0 years (IQR 45.0-77.0) and male patients accounted for 63.9% (2101/3287). Overall, 46.3% patients admitted for infectious disease, 39.1% for medical diseases, and 14.9% for surgical reason. Antimicrobials were used in 84.8% (2787/3287) of the patients on surveyed days. The HAI prevalence was 29.5% (965/3266) among surveyed patients with 922 patients with a single HAI episode and 43 patients with two or more HAI episodes. 15.6% (151/965) patients acquired their HAI during a previous hospital admission and 84.4% (814/965) patient acquired their HAI in the current hospital. A total of 726 pathogens were detected in patients with HAI, representing 59.4% (573/965) of patients with HAI. Data from the medical and surgical ICUs of H04 were collected separately but given their small size which are presented as one general ICU.

4.3.1 Antimicrobial use

Antimicrobial use was evaluated in all enrolled patients. The pooled proportion of patients receiving an antimicrobial at the time of the survey was 84.8% (2787/3287) and ranged from 60.4% to 99.8% between ICUs, with highest usage rates seen in tertiary ICUs (Figure 4 – 1). Interestingly nearly all patients admitted to the ICUs of H05 and H10 received an antimicrobial. H05 is a tertiary – surgical specialty hospital, with 91.7% ICU admissions for surgery with all patients intubated. H10 is a tertiary general hospital with 21.1% ICU admissions for surgery and 15.5% for infectious disease with 31.8% intubated patients. In addition, prevalence of HAI in H05 ICU was 60.9% while in H10 ICU was 6.9%. These factors could not explain why nearly 100% of patients received antibiotics in both ICUs. The lowest consumption was seen in H07 and H12. These hospitals were general provincial hospitals. 60.7% admissions to the ICU of H07 was for surgery and infectious diseases while that was 36.8% of the admissions to the ICU of H12. Prevalence of intubation and HAI in ICU of H07 was 55.9% and 14.5% while these in ICU of H12 was 22.4% and 16.1%,

respectively (Table A - 2 in Appendix A). These differences can not explain for the similar proportions of antibiotic use in these ICUs. The majority of patients was prescribed two antimicrobials (n=1343; 40.8%), followed by one microbial in 733 patients (22.3%), three in 552 patients (16.8%), and four in 159 patients (4.8%). Regarding antimicrobial combinations, the most common double combinations were: 3rd generation cephalosporins with fluoroquinolones (19.1%), carbapenems with fluoroquinolones (10.8%), and 3rd generation cephalosporins with aminoglycosides (7.8%). Combinations of three antimicrobials were: 3rd generation cephalosporins with fluoroquinolones and glycopeptides (13.6%), 3rd generation cephalosporins with fluoroquinolones and imidazole derivatives (6.0%). More details on antimicrobial combination and frequent use are presented in Table A - 3 and Table A - 4 in Appendix A.

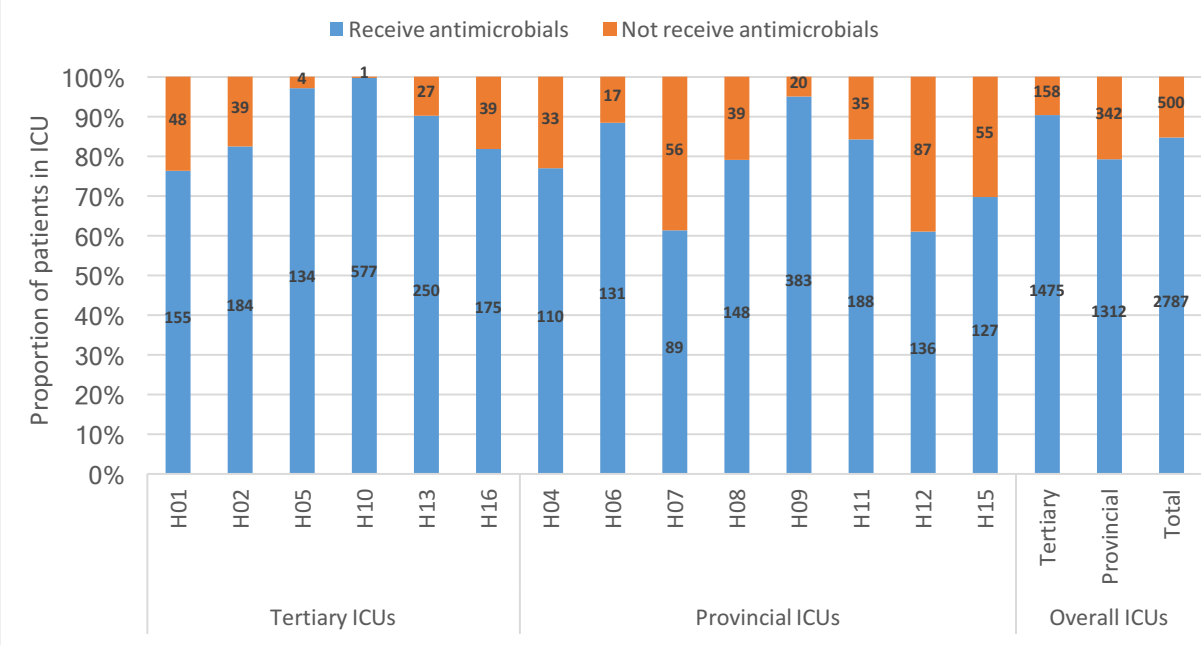


Figure 4 – 1. Proportion of surveyed patients using antimicrobials on surveyed days

On average, antimicrobial consumption was 173.7 DOT/100 PD, varying from 206.0 DOT/100 PD at tertiary ICUs and 141.9 in provincial ICUs. Consumption of antimicrobials ranged from the lowest 85.2 DOT/100 PD at ICU in H12 hospital to highest 274.7 DOT/100 PD at ICU in H10 hospital. The low antibiotic consumption at ICU of H12 may be explained by the low proportion of admissions due to surgery and infectious diseases (36.8%) and low

invasive procedure (22.4% intubated patients). However, it is difficult to explain the high antibiotic consumption at ICU of H10 because of low proportion of intubated patients (31.8%), central vascular catheter access (8.5%), HAI (6.9%), and admission due to surgery (21.1%) and infectious diseases (15.5%) (Table A - 2 in Appendix A). Antibiotic indications may provide more insights (see below). The three most common used antimicrobials were 3rd-generation cephalosporins, fluoroquinolones, and carbapenems, accounting for more than 50% of total DOT of all used antimicrobials. In total, consumption of 3rd-generation cephalosporins was 34.3 DOT/100 PD, fluoroquinolones 32.9 DOT/100 PD, and carbapenems 23.9 DOT/100 PD. More details are presented in Figure 4 - 2.

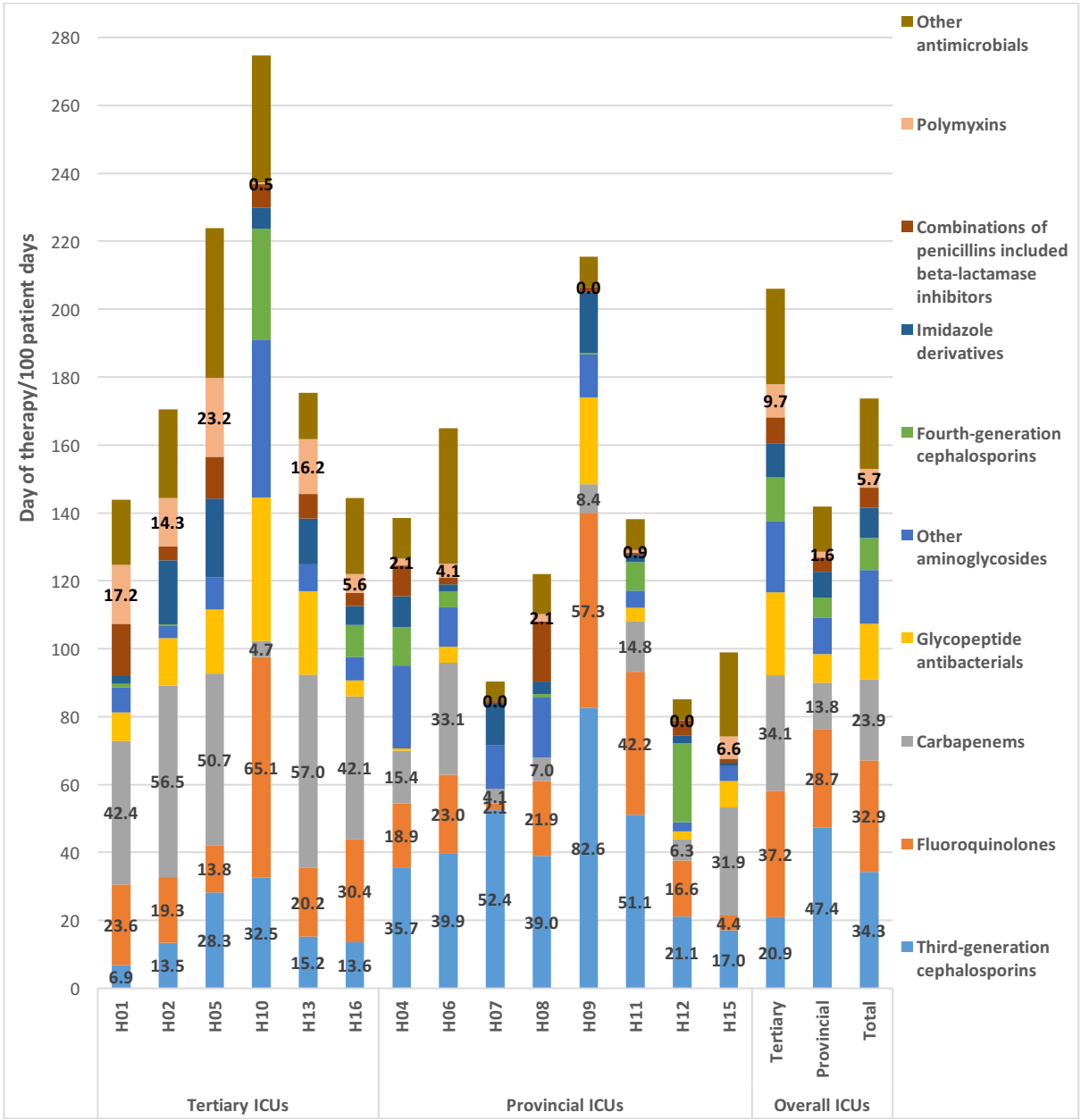


Figure 4 - 2. Antimicrobial consumption by class for each ICU

Analysing antimicrobial use by proportions: antimicrobials for systemic use (ATC group J01) accounted for 97.9% (5590/5711) of the total antimicrobials used. Of which, third generation cephalosporins, fluoroquinolones, and carbapenems were used most commonly - accounting for 20.1% (1126/5590), 19.4% (1082/5590), and 14.1% (786/5590), respectively. Among antibiotics used for HAI treatment, the most frequently used agents were carbapenems (22.9%; 432/1890), fluoroquinolones (16.0%; 302/1890), and 3rd generation cephalosporins (15.5%; 293/1890). Polymyxins (parenteral colistin) accounted for 3.3% (186/5590) of total use but was the fifth most frequently used agent for HAIs, reflecting the impact of drug resistance on choice of antimicrobials. (Figure. 4 - 3).

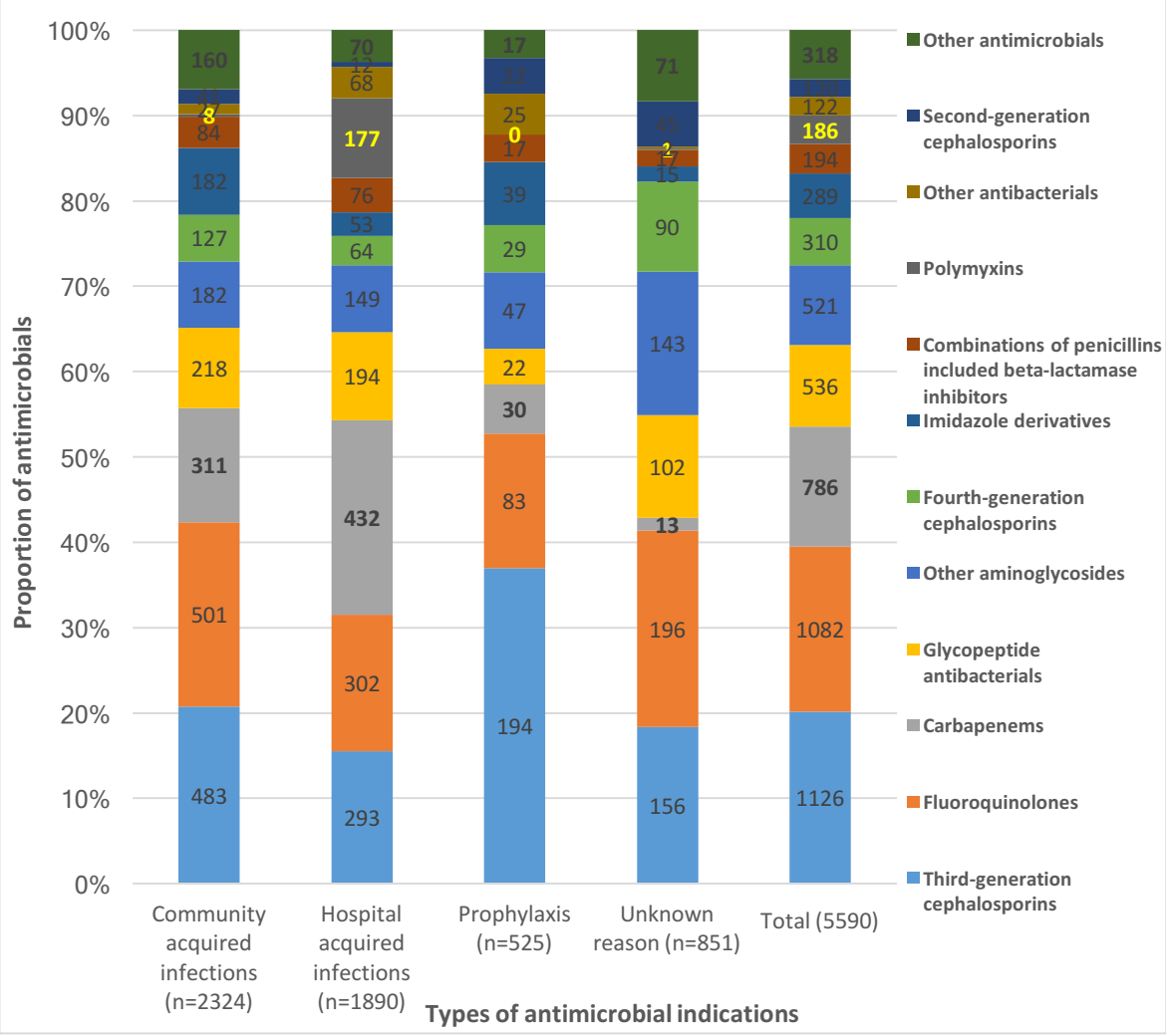


Figure 4 - 3. Antimicrobials used by types of indication

The type of infection was known for 76.2% (4348/5707) antimicrobial agents used. The most predominant infection was pneumonia, accounting for 63.1%, followed by intraabdominal sepsis (Table 4 – 1).

Table 4 - 1. Types of infections for which antimicrobials were administered

No.	Infection sites indicated antimicrobials	Frequency	Percentage
1.	Pneumonia	2857	63.1%
2.	Intraabdominal sepsis	391	8.6%
3.	Cellulitis, wound, deep soft tissue, not involving bone	338	7.5%
4.	Infections of the central nervous system	251	5.5%
5.	Gastrointestinal infections (e.g. salmonellosis, antibiotic associated diarrhoea)	154	3.4%
6.	Clinical sepsis (suspected bloodstream infection without lab confirmation/ results are not available, no blood cultures collected or negative blood culture), excluding FN	146	3.2%
7.	Laboratory confirmed bacteraemia	85	1.9%
8.	Acute bronchitis or exacerbations of chronic bronchitis	69	1.5%
9.	Symptomatic lower urinary tract infection (e.g. cystitis)	55	1.2%
10.	Symptomatic upper urinary tract infection (e.g. pyelonephritis)	52	1.1%
11.	Systemic inflammatory response with no clear anatomic site	36	0.8%
12.	Infections of ear, nose, throat, larynx and mouth	29	0.6%
13.	Obstetric or gynaecological infections, STD in women	24	0.5%
14.	Asymptomatic bacteriuria	17	0.4%
15.	Cardiovascular infections: endocarditis, vascular graft	15	0.3%
16.	Febrile neutropaenia or other form of manifestation of infection in immunocompromised host (e.g. HIV, chemotherapy etc) with no clear anatomical site	6	0.1%
	Total	**4525**	**100%**

Of the infectious indications, 41.8% (2386/5711) were community-acquired infections and 33.9% (1937/5711) HAIs. Non-infectious reasons for prescribing antibiotics were: prophylaxis (498/5711) and other (e.g. erythromycin for stimulating gastric kinetic, 38/5711) indications accounted for 9.4% (536/5711) and unknown indication accounted for 14.9% (852/5711). Prophylaxis and other indications was near 0% for the ICUs of H01, H08, and H15, likely explained by the fact that there was almost no admission to these ICUs for surgery. The high proportion (30.5%) of antibiotics use for prophylaxis in ICU of H07 hospitals may be due to similarly rate of ICU admission for surgical reason (35.2%). Antibiotic indication for community acquired infections ranged from 12.6% in ICU of H05 hospital to 71.1% in ICU of H08 hospital. These rates are relatively similar to the proportions

of ICU admission due to infection in these ICUs, 5.5% and 75.3% respectively. In most ICUs proportion of unknown indication for antibiotic use was generally under 5%, except for ICU of H11 (11.0%) and H10 (46.0%). Unknown indication here implies that there was no obvious convincing reason for antibiotic use. These high levels may be due to lack of antibiotic stewardship and guidelines on infection diagnosis and antibiotic use. More details are provided in Figure 4 - 4.

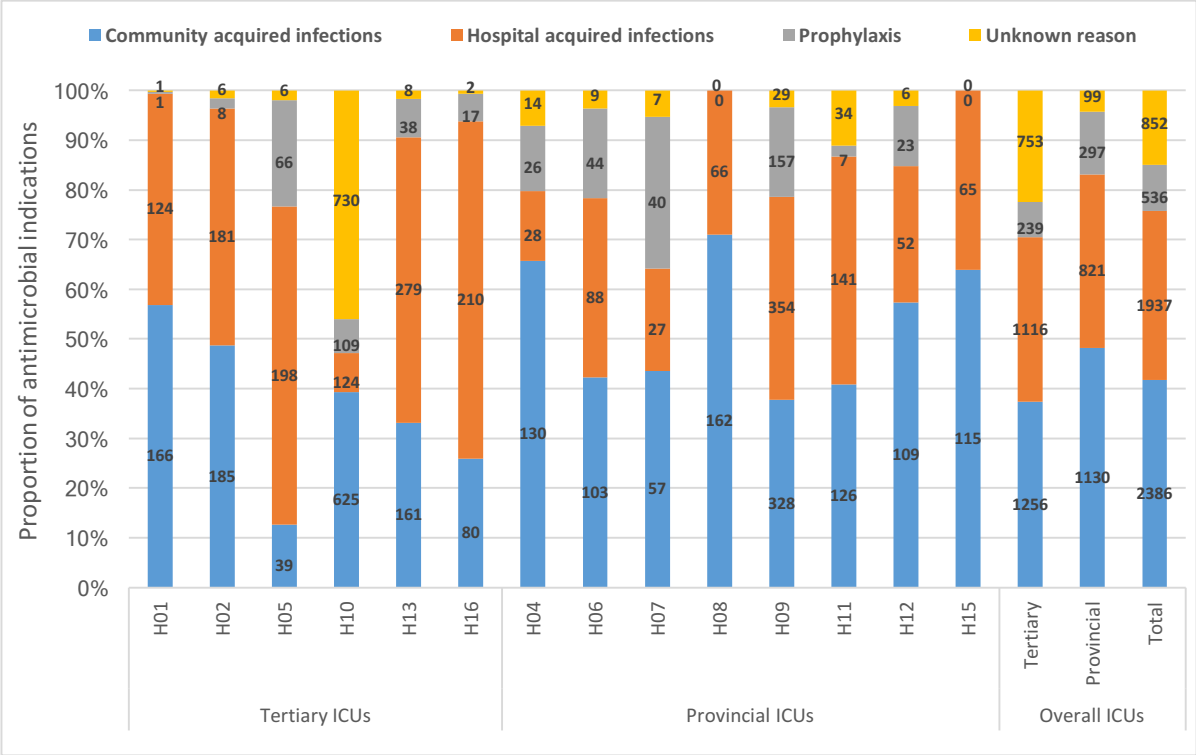


Figure 4 - 4. Proportion of antimicrobial indication types by the ICUs

4.3.2 Microbiological aetiology of HAIs

4.3.2.1 Microorganisms isolated from HAIs

In total, 726 pathogens for 601 HAIs were isolated in 573/965 (59.4%) patients with HAI. Pathogens isolated from pneumonia accounted for 80.9%, from BSI 6.1%, SSI 4.7%, UTI 3.4%, and other 4.7%. Most common pathogens of HAIs were *Acinetobacter* species 30.7% (*A. baumannii* 24.4%, *Acinetobacter* spp. 6.3%), *Klebsiella* species 16.4% (*K. pneumoniae* 11.6%, *Klebsiella* spp. 4.8%), *P. aeruginosa* 13.8%, *E. coli* 5.4%, and *S. aureus* 5.4%. These pathogens accounted for 71.7% of total pathogens for HAIs. (Table 4 - 2)

Table 4 - 2. Microorganisms associated with HAIs

Microorganisms	Pathogens isolated from hospital acquired infections				
	All HAIs	Pneumonia	Blood stream infections	Surgical site infections	Urinary tract infections
	n (%)	n (%)	n (%)	n (%)	n (%)
Gram-negative bacteria	**611 (84.2)**	**516 (87.9)**	**28 (63.6)**	**25 (73.5)**	**15 (60.0)**
Acinetobacter spp.	223 (30.7)	197 (33.6)	10 (22.7)	2 (5.9)	5 (20.0)
Pseudomonas aeruginosa	100 (13.8)	92 (15.7)	2 (4.5)	3 (8.8)	0
Klebsiella pneumoniae	84 (11.6)	68 (11.6)	5 (11.4)	8 (23.5)	1 (4.0)
Escherichia coli	39 (5.4)	20 (3.4)	6 (13.6)	4 (11.8)	3 (12.0)
Klebsiella spp.	54 (7.4)	44 (7.4)	2 (4.5)	3 (8.8)	1 (4.0)
Providencia spp.	28 (3.9)	25 (4.3)	0	2 (5.9)	0
Achromobacter spp.	18 (2.5)	17 (2.9)	0	1 (2.9)	0
Stenotrophomonas maltophilia	6 (0.8)	6 (1.0)	0	0	0
Gram-negative bacilli others	55 (7.6)	43 (7.3)	3 (6.8)	2 (5.9)	5 (20.0)
Gram-negative cocci other	4 (0.6)	4 (0.7)	0	0	0
Gram-positive bacteria	**104 (14.3)**	**65 (11.1)**	**15 (34.1)**	**9 (26.5)**	**7 (28.0)**
Staphylococcus aureus	39 (5.4)	28 (4.8)	6 (13.6)	3 (8.8)	0
Staphylococcus spp.	19 (2.6)	11 (1.9)	6 (13.6)	0	1 (4.0)
Streptococcus spp.	11 (1.5)	9 (1.5)	0	1 (2.9)	0
Enterococcus spp.	29 (4.0)	11 (1.9)	3 (6.8)	5 (14.7)	6 (24.0)
Gram-positive bacilli other	6 (0.8)	6 (1.0)	0	0	0
Fungi	**11 (1.5)**	**6 (1.0)**	**1 (2.3)**	**0**	**3 (12.0)**
Candida spp.	10 (1.4)	5 (0.8)	1 (2.3)	0	3 (12.0)
Other fungi	1 (0.1)	1 (0.2)	0	0	0
Total isolates	**726 (100)**	**587 (100)**	**44 (100)**	**34 (100)**	**25 (100)**

4.3.2.2 Antimicrobial resistance of HAI pathogens

Among 726 isolates, susceptibility was available for 705 isolates (97.1%). Antimicrobial resistance was common in these isolates. Resistance to carbapenem accounted for 86.8% *Acinetobacter* spp., 55.7% *P. aeruginosa,* and 14.9% *K. pneumoniae.* Resistance to 3rd generation cephalosporin accounted for 67.3% of all Enterobacteriaceae isolated. More than 75% of the *S. aureus* isolates were methicillin resistant and up to 57.7% of the *Enterococcus* spp. were resistant to glycopeptides. More details about aetiology for all HAI and some specific HAIs are presented in Table 4 – 3.

Table 4 - 3. Antimicrobial susceptibilities of HAI associated microbes

Pathogens for HAI originated in surveyed hospitals	Antimicrobials resistance				Total, n = 705 (%)
Enterobacteriaceae	**C3-S, Car-S**	**C3-R, Car-S**	**C3-R, Car-R**	**UNK**	**235 (33.3)**
Klebsiella pneumoniae, n (%)	21 (28.4)	42 (56.8)	11 (14.9)	7	81 (11.5)
Escherichia coli, n (%)	15 (40.5)	20 (54.1)	2 (5.4)	2	39 (5.5)
Klebsiella spp., n (%)	17 (30.1)	33 (62.3)	3 (5.7)	0	53 (7.5)
Providencia spp., n (%)	11 (40.7)	15 (55.6)	1 (3.7)	0	27 (3.8)
Other Enterobacteriaceae, n (%)	9 (28.1)	19 (59.4)	4 (12.5)	3	35 (5.0)
Gram-negative bacilli	**Car-S**	**Car-R**		**UNK**	**362 (51.3)**
Acinetobacter spp., n (%)	28 (13.2)	184 (86.8)		10	222 (31.5)
Pseudomonas aeruginosa, n (%)	39 (44.3)	49 (55.7)		10	98 (13.9)
Other Gram-negative bacilli, n (%)	NA	NA			42 (6.0)
Staphylococcus spp.	**Oxa-S**	**Oxa-R**		**UNK**	**56 (7.9)**
Staphylococcus aureus, n (%)	9 (24.3)	28 (75.7)		2	39 (5.5)
Staphylococcus spp., n (%)	7 (63.6)	4 (36.4)		6	17 (2.4)
Enterococcus spp.	**Glyco-S**	**Glyco-R**		**UNK**	**29 (4.1)**
Enterococcus spp., n (%)	11 (42.3)	15 (57.7)		3	29 (4.1)
Other microorganisms					**23 (3.3)**
Streptococcus spp., n (%)					8 (1.1)
Other bacteria, n (%)					10 (1.4)
Candida spp., n (%)					5 (0.7)
Total isolates					**705 (100)**

C3-R: resistant to 3rd generation cephalosporins, C3-S: susceptible to 3rd generation cephalosporins, Car-R: resistant to carbapenems, Car-S: susceptible to carbapenems, Glyco-R: resistant to glycopeptides, Glyco-S: susceptible to glycopeptides, Oxa-S: susceptible to oxacillin, Oxa-R: resistant to oxacillin, UNK: unknown, NA: not assess.

Pathogen of specific HAI

Pathogens with susceptibility data isolated from patients with hospital-acquired pneumonia (HAP) were: *A. baumannii* 26.5%, *P. aeruginosa* 15.7%, and *K. pneumoniae* 11.2% with carbapenem resistance levels of 89.7%, 55.6%, and 15.3%, respectively. Among Enterobacteriaceae other than *K. pneumoniae*, 3rd generation cephalosporin resistance ranged from 60.0% to 72% and carbapenem resistance ranged from 3.8% to 11.1% of isolates. Methicillin resistant *S. aureus* accounted for 76.9% (20/26) of *S. aureus* isolated. Most common pathogens for hospital acquired blood stream infections were gram negative bacilli (65.8%). 7/8 of *A. baumannii* was resistant to carbapenem, 3/6 *E. coli* and 3/5 *K. pneumoniae* were resistant to 3rd generation cephalosporins, and 5/6 *S. aureus* resistant to methicillin. The majority of pathogens from SSI and UTI were also gram negative bacilli, 73.5% and 68.2% respectively, and 44.4% Enterobacteriaceae resistant to 3rd in both SSI and UTI. All (2/2) *A.*

baumannii isolated in SSI were susceptible to carbapenems but all (5/5) *A. baumannii* for UTI were resistant to carbapenems.

Pathogen of HAI originated from surveyed hospitals

Antimicrobial resistance of pathogens for HAIs originated from surveyed hospitals are presented in Table A – 5 in Appendix A. Proportion of antimicrobial resistance was high similar to total pathogens for HAI. In tertiary ICUs, carbapenem resistance was 94.1% to 100% in *A. baumannii,* 33.3% to 100% in *P. aeruginosa,* and 0% to 33.0% in *K. pneumoniae*. In provincial ICUs, carbapenem resistance ranged from 0.0% to 83.3% in *A. baumannii*, 0.0% to 83.3% in *P. aeruginosa,* and 0.0% to 50.0% in *K. pneumoniae.* Nearly 100% of *A. baumannii* resistant to carbapenems was seen at ICUs using more than 140 DOT/100 PD. Association between total antimicrobial use and some main antibiotic resistance for each ICU were presented in Figure 4 – 5.

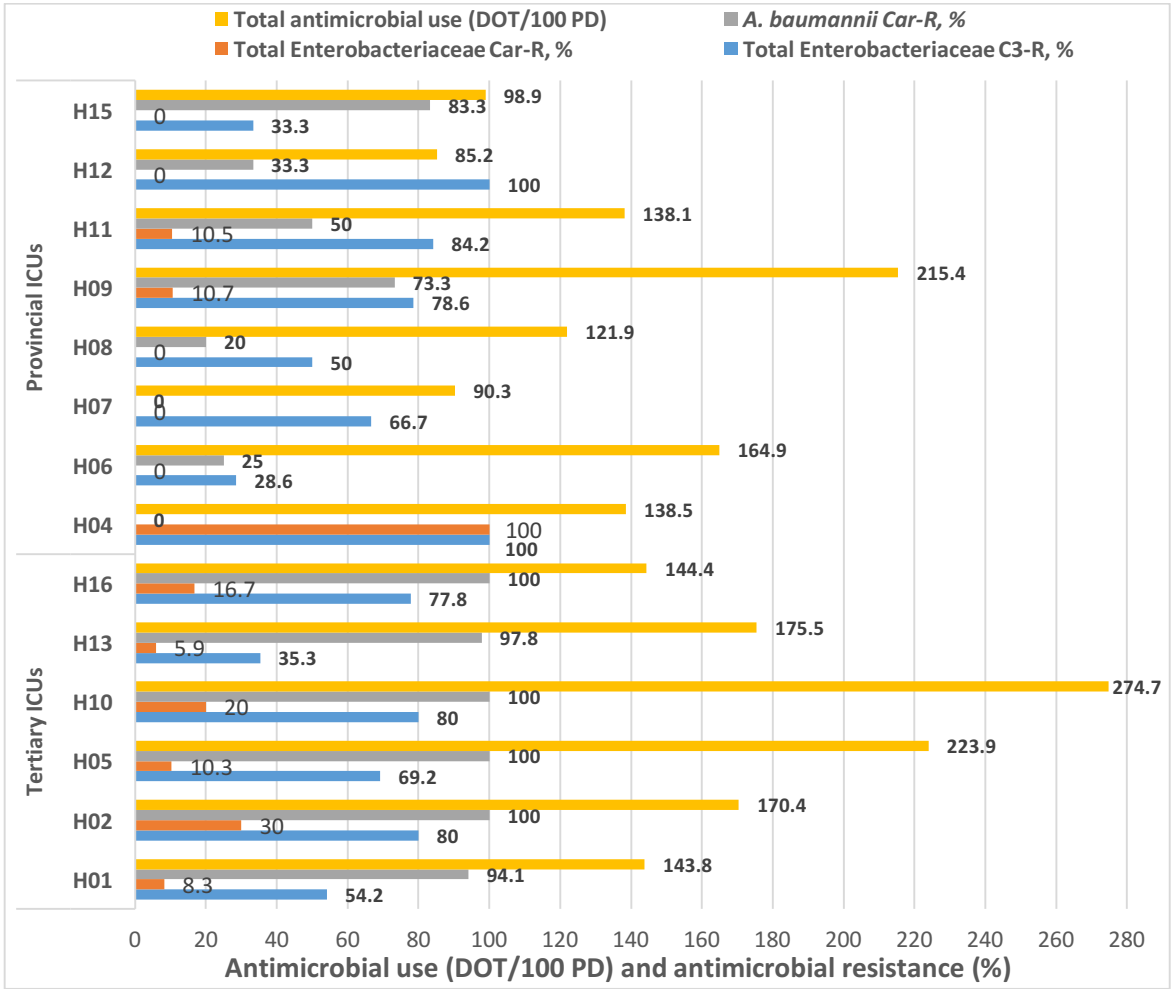


Figure 4 – 5. Total antimicrobial use and main antibiotic resistance at ICUs

Among 241 patients with a carbapenem resistant strain, 30 patients were given monotherapy (11 with polymyxins, 19 with other antibiotics), 117 patients were given combination therapy with polymyxins, and 94 patients were given combination therapy without polymyxins. 53.1% (128/241) patients with carbapenem resistant infections were given polymyxins. Among 117 patients with combination therapy including polymyxins, 79 patients were treated with two antibiotics, 35 patients with three antibiotics, and three patients with four antibiotics. Most common antibiotic combinations with polymyxins were: carbapenems (53.8%; 63/117), cefoperazone (20.5%; 24/117), and piperacillin & enzyme inhibitor (6.8%; 8/117). Among 94 patients who were not treated with polymyxins, 63 patients were given two antibiotics and 31 patients given three or more antibiotics. The most common antibiotics in these combinations were carbapenems 57.4% (54/94), vancomycin 28.7% (27/94), and levofloxacin 25.5% (24/94). Overall there were many different treatment strategies for carbapenem resistant infections, likely due to the lack of a national guideline for these infections. More details were presented in Table A - 6 in Appendix A.

4.4 Discussion

4.4.1 Antimicrobial use

There were two levels of ICUs (tertiary and provincial ICUs) and three types of ICUs (H05 is surgical, H01 and H15 is infectious, and the others are mixed ICUs) in our study. This PPS illustrates that a high proportion of ICU patients receive antimicrobials (84.8%), ranging from 60.4% to 99.8% per individual ICUs, and that the rate at tertiary ICUs (90.3%) was higher than at provincial ICUs (79.3%) (Figure 4 – 1). The overall 84.8% of the ICU patients on antimicrobials in this study is also higher than the 56.5% in European ICUs [5] and the reported maximum of 77.3% at surgical ICUs in the United States in 2011 [98].

Looking for explanations for this finding, ICUs with the highest proportion of patients on antimicrobial use were a mixed ICU (99.8% at H10) and a surgical ICU (97.1% at H05).

Interestingly, not specialized ICUs on infectious diseases (76.4% at H01 and 69.8% at H15) had the highest rates, though this would be expected. Furthermore, the lowest proportion of patients prescribed antimicrobials amongst the tertiary hospitals was in one of the ICUs specializing in infection (H01) and an ICU of a provincial hospital specializing in infection (H15) was the third lowest among provincial ICUs. These findings suggest that it is not the nature of the admissions to the ICUs that is causing the high rate of antibiotic use. Possibly, the fact that hospitals specialized in infectious diseases have a better understanding of treating infections, may explain the low use in these ICUs. This phenomenon was more clearly seen when seeing data on antimicrobial use by DOT/100 PD (Figure 4 – 2). Overall, antimicrobial use at Vietnam ICUs in the current study was 173.7 DOT/100 PD. Antimicrobial use at H10 ICU was the highest (274.7 DOT/100 PD) and was about double that of H01 ICU (143.8 DOT/100 PD) and triple that of H15 ICU (98.9 DOT/100 PD), the two infectious disease speciality ICUs. This could mean that antimicrobial use at these two specialized ICUs were more strictly than the other ICUs so that there was less unnecessary use of antimicrobials than the other ICUs. Of note both of these sites have had a longstanding relationship with Oxford University, which may also have influenced prescribing behavior, though many of the large hospitals also have established a longstanding relationship with overseas institutions. Data on indications for antimicrobial use (Figure 4 – 3) showed almost no other indications for antimicrobial use except for infection treatment (community and hospital acquired infections) at these two ICUs while at the other ICUs, with the exception of H08, indications for prophylaxis and unknown reason ranged from under 10% to more than 50%. Other reason for this finding could be that other ICUs are surgical and mixed ICUs, where possibly more appropriate than is the case for two ICUs specialized in infectious diseases. However, the considerable proportion of antimicrobial use with unknown reason occurring in the other ICUs, suggest that the use of antimicrobials at these ICUs was less restricted than at two infection ICUs. These data suggest that involvement of specialists in infectious diseases participate in ICU work could lead to a decrease in antimicrobial use in ICUs and should be

investigated further. At present, Vietnamese ICUs have no regularly consultations from specialists in infectious diseases, or regular input from microbiologists.

Antimicrobial use measured by DOT/100 PD also shows that the Vietnamese rates are significantly higher in ICUs from developed countries. In our study, pooled antimicrobial consumption of 173.7 DOT/100 PD is higher than that of 136.8 DOT/100 PD in ICU in a single center study in the United States in 2010 [164] and than that in German ICUs in 2012 with ~80 DDD/100 PD [97]. This could be explained by a higher infectious disease burden in Vietnam ICUs: 46.3% of patients were admitted to ICU for an infectious disease in addition with 12.9% (424/3287) patients acquired HAI after ICU admission [chapter 3]). In the United States, only 17.2% of elderly patients admitted to ICU in 2010 was due to an infectious disease [165]. The high burden of infectious diseases in Vietnamese ICUs is a combination of poor infection control practices leading to high rates of HAI (Chapter 3) and the general burden of tropical infectious diseases in community [166]. As a result, infectious diseases are on the fifth position in Vietnam on the disease burden ranking after diseases on respiratory, circulatory, digestive, and obstetric problems [101]. Besides the high burden of infectious diseases, there are also high rates of patients on antimicrobials, both appropriate and inappropriate. A significant proportion of antimicrobial use in Vietnam is due to unknown reason, 14.9% in overall and up to 46.0% in an ICU (Figure 4 – 3). These situations require urgently a systematic antimicrobial stewardship for Vietnam ICUs and also improve hygiene in the hospital and in the community.

Usually, antimicrobial use would decrease over time because of improvement in infection control practice, increased awareness on antimicrobial resistance, and more accurate diagnosis of infectious diseases. However, antimicrobial consumption at ICUs in the current study was higher than reported in a previous study in ICUs of three hospital in the North Vietnam in 2007, which ranged from 76 to 99.9 DDD/100 PD with average of 81.1 DDD/100 PD [146]. This difference could be due to ICU selection for these studies and also difference in study

methods to measure antimicrobial use. Antimicrobial consumption in the current study is significantly lower than that for whole hospital of 274.7 DDD/100 PD in average of 15 hospitals, ranging from about 130 at H15 to 466 DDD/100 at H08 among non-pediatrics hospitals in 2008 [157]. This is striking as ICUs in general have the highest antimicrobial consumption in a hospital. This needs to be investigated further to find out underlining reasons for future interventions to achieve accurate antimicrobial use.

Pneumonia is a common indication for antimicrobial use, accounting for 63.1% of total antimicrobials used for infection treatment. While in acute hospitals in European, respiratory tract infections only accounted for 32.8% of total antimicrobial use [5]. This reflect high burden of respiratory infection in ICUs in Vietnam, which should be prioritized in developing antibiotic stewardship and infection control measures.

The proportion of carbapenem use in the current study for treatment of HAI is much higher than that used for HAIs in European hospitals: 22.9% versus 9.4% respectively [5]. Although the European data is for HAI treatment in whole European hospitals (not only ICU), it still reveals the high carbapenems use in Vietnamese ICUs, a last resort for infection treatment. Carbapenem use in our study by 23.9 DOT/100 PD (Figure 4 – 2) is a slightly higher than that of 19.6 DOT/100 PD in one ICUs in the United States in 2010 [164]. Reasons for high carbapenem use could be: the high rate of bacteria resistant to antimicrobials, high disease severity of ICU patients, inadequate and accurate facilities for diagnosis of bacterial infections, and inadequate antimicrobial stewardship. All these aspects should be addressed to reserve this last resort as well as other antimicrobials.

4.4.2 Pathogens for HAIs

In our study, Gram-negative bacteria were the most common isolated pathogens from patients with HAI. This is similar to studies in low and middle income countries [10, 138, 144]. Another study in South Korea and India showed that *S. aureus,* a Gram-positive bacterium,

accounted for a considerable proportion of pathogens for HAI in ICUs, 34.9% and 25.0% respectively [52]. However, in our study *S. aureus* accounted for just 4.8%, while Gram negative bacteria (*Acinetobacter* spp., *P. aeruginosa*, and *K. pneumonia*) were major pathogens for all HAIs accounting for 56.1% (Table 4 - 2) with high proportions of carbapenem resistance (Table 4 - 3). In the current study, *Acinetobacter* spp. was the most common isolate (30.7%) for HAI and higher compared to 19.2% in other ICUs in Asia, and 3.7% in North America [167]. *A. baumannii* and *P. aeruginosa* accounted for 44.5% of total isolates for HAIs. This proportion is considerable higher than that of 34.1% in Turkey in 2007 – 2008 [168] and 34.6% in a previous study at three ICUs in Vietnam in 2007 [146]. Carbapenem resistance among *A. baumannii* and *P. aeruginosa* increased compared to 69.1% and 44.4% sequentially in previous study in Vietnam ICUs in 2007 [146]. The high prevalence of carbapenem resistance could be caused by a part from the high prevalence of antibiotic use which leads to selection for antibiotic resistant bacteria. And these figure could be due to selection bias from the design of point prevalence survey; patients with long stay are over represented and may be surveyed during the second or even later episode of HAI. Consequently, high prevalence of carbapenem resistance leads to an increased colistin use [140] and subsequent emergence and spread of colistin resistance.

The high rates of MRSA and glycopeptide resistant enterococci are also a major concern. However, the burden of Gram-positive infections as a cause of HAI is relatively low as compared to Gram-negative infections. High level of resistant to last resort of antimicrobials could be consequence from poor infection control practice and high antimicrobial consumption. Antimicrobial resistance also leads to a high consumption of last resort antimicrobials. Antimicrobial stewardship programmes and the deployment of alternatives to carbapenems may help to slow the development of further resistance to the remaining active antibiotics [169] and need to be evaluated in this context. Additionally, suitable infection control measures must be complied and monitored strictly. However, to achieve effectivity of these interventions all basic facilities and resources for doing these must be supplied, such as

infrastructure of ICU, facilities for infection diagnosis, care and infection control, adequate human resource achieving requirement of working in ICU.

In conclusion

High antimicrobial consumption, with about one third for HAIs treatment, and around 15% of antimicrobial use for unknown reason illustrate the urgent need for antimicrobial stewardship programmes and also infection control programmes in Vietnamese ICUs. The majority of infections in ICUs was pneumonia, which should be prioritized in future control strategies.

Chapter 5

Risk factors for ventilator-associated pneumonia and ventilator-associated respiratory infections in Vietnamese intensive care units

5.1 Introduction

Ventilator associated pneumonia (VAP) is one of the ventilator associated respiratory infections (VARI) which occurs in a significant proportion of ventilated patients in ICUs. These infections are reported to have important consequences, including prolonged ventilation time, length of ICU and hospital stay, hospital cost, and increased mortality [46, 48, 51, 67, 170-172]. As a result, there have been many efforts to reduce the occurrence of these infections [173-175]. Despite these efforts, reported VAP prevalence rates are often high. An international study across 56 ICUs in 11 countries in 2012 showed an overall VAP prevalence of 15.6% with an incidence of 13.6 episodes/1000 ventilation days. Prevalence for the USA was reported as 13.5%, with incidence of 12.1 episodes/1000 ventilation days. In Europe prevalence was higher at 19.4% and incidence of 15.0 episodes/1000 ventilation days. Latin America and Asia Pacific had similar incidence to USA of 13.6 episodes/1000 ventilation days and prevalence of 13.8% and 16.0% respectively [42]. However there is considerable variation in reported figures particularly in the United States where other studies reported lower VAP incidences: 4.4 episodes/1000 ventilation days in a specialist burns ICU, 1.0 episodes/ 1000 ventilation days in a major medical teaching hospital ICU, 1.6 episodes/1000 ventilation days in a mixed medical/surgical teaching hospital ICU, and 2.2 episodes/ 1000 ventilation days in a surgical teaching hospital ICU [176].

In low and lower middle income countries, few data are available. A systemic review of HAI in developing countries between 2006 and 2008 reported VAP to be the most frequent HAI in critical care units, with an incidence of 22.9 episodes/1000 ventilation days, nearly eight folds

higher than in the USA. They also noted that high-quality studies tended to report higher rates. [10].

In Vietnam, there is no national surveillance system for HAI, but studies on HAI in ICUs have shown that the point prevalence of HAI in ICUs ranged from 19.3% to 31.3% [110, 112, 114-117] and that VAP incidence ranged from 17.4% to 56.6% [118, 119, 121] and VAP incidence density ranged from 11.7 episodes to 61.3 episodes per 1000 ventilation days [116, 118, 119]. Surveillance on hospital-acquired infections (HAI) in intensive care units of 14 tertiary and provincial hospitals across Vietnam in 2013, conducted as part of this thesis, showed that the prevalence of HAI was 29.5%, of which hospital-acquired pneumonia accounted for approximately 80% (chapter 3) [120].

These sparse data suggest that the burden of VAP is relatively high in intensive care units in Vietnam. However, more systematic high quality data is needed to inform policy makers and doctors to enable optimal prevention and management of this issue. This chapter describes the results of a study that systemically assessed the incidence and risk factors of VARI, including VAP and other ventilator-associated respiratory infections, at three referral hospitals in Hanoi and Ho Chi Minh City, Vietnam.

5.2 Methods

A prospective, observational study of the clinical epidemiology and etiology of VAP was performed from November 2013 to May 2015 on the Intensive Care Units of the National Hospital for Tropical Diseases (NHTD) and from July 2014 to May 2015 on the Intensive Care Units of Bach Mai Hospital (BMH), both in Hanoi, and from October 2014 to November 2015 on the Intensive Care Units of Hospital for Tropical Diseases (HTD) in Ho Chi Minh City, Vietnam. The detailed methods are presented in chapter 2.

5.3 Results

5.3.1 Characteristics of study sites

The National Hospital for Tropical Diseases (NHTD) is a teaching hospital for infectious diseases with 280 beds located in Hanoi. NHTD provides in-hospital care for more than 7300 patients annually. The ICU has 21 beds (18 ventilated beds) in 2 single rooms and 5 common room (distance between beds is about 60 cm in common room), 7 doctors and 28 nurses in total, and provides medical services for about 500 ICU patients per year with mean ICU stay of about 9 days. Bach Mai Hospital (BMH) is the largest hospital in Hanoi with 1900 beds, provides in-hospital care for more than 114,000 patients annually. BMH ICU has 38 beds (based on 30 beds of origin design, so that the distance between beds is also about 60 cm), managed by total 13 doctors and 55 nurses, and provides medical services for around 1,300 ICU patients per year with mean ICU stay of around 10 days. The last study site is the ICU in Hospital for Tropical Diseases (HTD) in Ho Chi Minh city. There are 550 beds in this hospital for about 42000 inpatients annually. HTD ICU has 23 beds with 8 doctors and 48 nurses serving 1500 ICU patients per year with mean ICU stay of about 16 days. Like NHTD, HTD serves as an infectious disease referral centre and only admits patients where the predominant problem is perceived to be infection. All sites provided advanced respiratory support, haemodynamic support and renal support. Extracorporeal membrane oxygenation (ECMO) was available in one site at the time of this study (BMH), though was not commonly used. In these ICUs, alcohol hand rub is available at the bedside, and sterile technique and maximized barrier precaution are prerequisite for all invasive procedures. Tracheostomy is performed on ward by ICU staff in most cases. Antibiotic guidelines are available and antibiotic use is routinely evaluated at these ICUs, however in contrast with Western units there is no microbiologist visiting the ICUs or de-escalation in commonly practice.

5.3.2 Common characteristics of patients

In total there were 453 patients enrolled in the study from November 2013 to November 2015. Three tetanus patients were excluded when their clinical research forms and medical records were reviewed as it was clear they had been admitted with suspected VAP. One patient withdrew from the study and 75 other patients were excluded from analysis due to: duration of ventilation of less than 48 hours (n = 69) and treatment with ECMO during the study period (n=6). Thus 374 patients were eligible for analysis, of which 161 (43.1%) were from NHTD, 61 (16.3%) from BMH, and 152 (40.6%) from HTD. Among 374 patients in analysis, 232 (62.0%) patients had medical insurance and 142 (38.0%) patients did not. This means that the sample size of 600 was not reached, due to unanticipated low recruitment rate and lack of funding to extend the study period.

5.3.2.1 Demographics

Among the 374 patients in final analysis, male gender was predominant with 267 patients accounting for 71.4% (267/374). Patients' age ranged widely from 16 years to 94 years with a median (IQR) of 52 (38 – 64) years (Table 5-1, Figure 5-1). There was a total of 18 patients admitted to ICU after surgery, of whom 10 had undergone emergency operations and 8 underwent elective operations. APACHE II scores (available for 341 patients at enrolment) ranged from 0 to 31 points with median (IQR) of 10 (6 – 15) points, and 330 patients had SOFA score ranging from 0 to 17 points with median (IQR) of 4 (2 – 7) points. Old age (defined as the proportion aged over 60 years) and gender were not significantly different between three study sites. Differences in SOFA and APACHE II score of patients were statistically significant between NHTD and BMH in comparison with HTD but not statistically significant between NHTD and BMH. (Table 5 - 1).

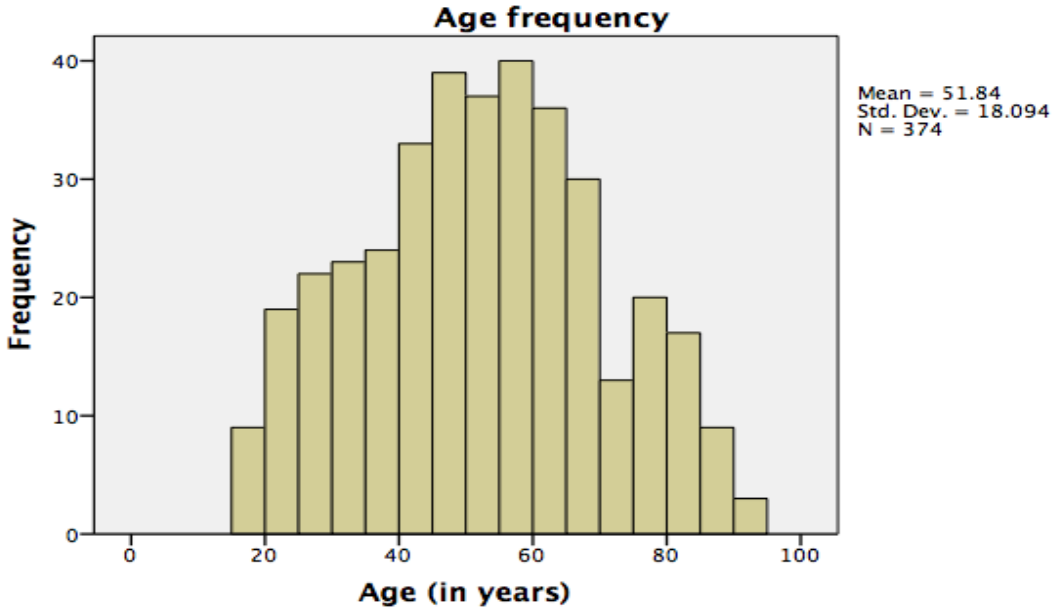


Figure 5 – 1. Age distribution of enrolled patients

5.3.2.2 Comorbidities

There were 144 (38.5%) patients with a total of 200 comorbidities, of whom, 98 patients had one comorbidity, 42 patients had two comorbidities, and 6 patients had three comorbidities. The proportion of patients with comorbidities was significantly different between three study sites. The highest proportion of comorbidities were reported in patients admitted to Bach Mai hospital (73.8%), followed by NHTD (46.3%), and HTD (16.4%) (Table 5 – 1). The most common comorbidities were alcoholism (28%), diabetes mellitus 18%, and chronic pulmonary diseases (12%) (Figure 5 - 2).

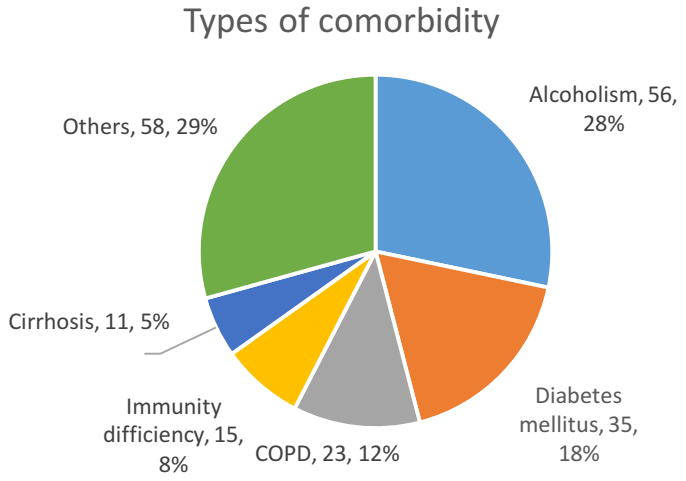


Figure 5 - 2. Proportion and type of comorbidities in study patients

Table 5 - 1. Patient characteristics by study site

Demographics	Total (n=374)	NHTD (n=161)	BMH (n=61)	HTD (n=152)	P value[1]	P value[2]	P value[3]
APACHE II score, median (IQR), mean ± SD	10 (6 – 15), 10.9 ± 6.0	11 (7 – 15), 11.5 ± 6.1	13 (9.3 - 17), 13.2 ± 5.3	8 (5 – 12), 9.2 ± 5.8	0.058[a]	0.001[a]	<0.0005[a]
SOFA score, median (IQR), mean ± SD	4 (2 – 7), 5.1 ± 3.9	5 (3 – 9), 6.3 ± 4.0	5.5 (3 – 7.3), 5.9 ± 3.7	3 (1 – 5), 3.7 ± 3.6	0.754[a]	<0.0005[a]	<0.0005[a]
Age, median (IQR), mean ± SD	52 (38-64), 51.8 ± 18.1	52 (42-62), 52.0 ± 16.6	56 (42-67.5), 55.1 ± 18.0	50 (34-65.8), 50.4 ± 19.5	0.223[a]	0.354[a]	0.090[a]
Ages > 60 years, n (%)	119 (31.8)	47 (29.2)	23 (37.7)	49 (32.2)	0.258[b]	0.624[b]	0.522[b]
Male gender, n (%)	267 (71.4)	116 (72.0)	42 (68.9)	109 (71.7)	0.623[b]	1.000[b]	0.739[b]
Comorbidity, n (%)	144 (38.5)	74 (46.3)	45 (73.8)	25 (16.4)	< 0.0005[b]	< 0.0005[b]	< 0.0005[b]
Alcoholism, n (%)	56 (15.0)	42 (25.6)	13 (20.6)	1 (0.7)	0.492[b]	< 0.0005[b]	< 0.0005[b]
Diabetes mellitus, n (%)	35 (9.4)	14 (8.3)	14 (22.2)	7 (4.6)	0.007[b]	0.178[b]	< 0.0005[b]
Chronic pulmonary diseases, n (%)	23 (6.1)	7 (4.2)	13 (20.6)	3 (2.0)	< 0.0005[b]	0.338[b]	< 0.0005[b]
Immune deficiency[c], n (%)	15 (4.0)	11 (6.5)	1 (1.6)	3 (2.0)	0.187[b]	0.053[b]	1.000[b]
Cirrhosis, n (%)	11 (2.9)	10 (6.0)	0	1 (0.7)	0.065[b]	0.011[b]	1.000[b]

[1] NHTD and BMH, [2] NHTD and HTD, and [3] BMH and HTD; [a] Mann Whitney U test, [b] Fisher's Exact test; [c] Including long term steroid use, chemotherapy, AIDS

5.3.2.3 Medical factors before and at ICU admission

In this study the majority (75.1%) of patients were transferred from other hospitals to the study sites. Proportions of transferred patients were statistically significant different between the three study sites. Transfer was particularly common at NHTD (88.8% of patients) and HTD (77%) as compared with BMH (34.4%). Most commonly patients first presented to provincial hospitals (46.3%), less commonly tertiary hospitals (15.8%). Twelve percent of patients were intubated before admission to the study sites, this was statistically significant higher at NHTD (21.7%) and BMH (11.5%) in comparison with at HTD (2.0%). Patients with a previous hospital admission or antibiotic use within 90 days before this illness accounted for 11.0% and 6.7% of all patients, respectively. 86.4% of patients already received

antibiotics on ICU admission: highest at NHTD (92.5%) and lowest at HTD (78.9%). (Table 5 - 2).

Table 5 - 2. Medical factors before and at ICU admission by study site

Interventions		**Total (n = 374)**	**NHTD (n = 161)**	**BMH (n = 61)**	**HTD (n = 152)**	**P value[1]**	**P value[2]**	**P value[3]**
Inpatient in last 90 days, n (%)		41 (11.0)	24 (14.9)	10 (16.4)	7 (4.6)	0.835	0.002	0.009
Antibiotic use in past 90 days, n (%)		25 (6.7)	12 (7.5)	8 (13.1)	5 (3.3)	0.197	0.135	0.011
Hospital transfer for this illness, n (%)		281 (75.1)	143 (88.8)	21 (34.4)	117 (77.0)	< 0.0005	0.006	< 0.0005
Previous hospital type, n (%)	Tertiary	59 (15.8)	51 (31.7)	2 (3.3)	6 (3.9)			
	Province	173 (46.3)	72 (44.7)	15 (24.6)	86 (56.6)			
	District	49 (13.1)	20 (12.4)	4 (6.6)	25 (16.4)			
Intubated before admission to study site, n (%)		45 (12.0)	35 (21.7)	7 (11.5)	3 (2.0)	0.088	< 0.0005	0.007
Antibiotic use on ICU admission[a], n (%)		323 (86.4)	149 (92.5)	54 (88.5)	120 (78.9)	0.420	0.001	0.119

[1] NHTD and BMH, [2] NHTD and HTD, and [3] BMH and HTD (Fisher's Exact Test).
[a] Excludes anti-tuberculous and anti-viral medication

5.3.2.4 Admission diagnosis

In this study, more than 90% of patients were admitted for an infectious disease. The most common reasons for admission were: tetanus (132 patients, 35.3%), pneumonia (73 patients, 19.5%), central nervous system (CNS) infection (60 patients, 16.0%), septic shock (28 patients, 7.5%), and sepsis (27 patients, 7.2%). The proportion of these diagnoses were different between the three study sites. Common diseases at NHTD were: pneumonia (29.8%), tetanus (22.4%), CNS infections (21.1%) and septic shock (16.1%). In BMH these were: pneumonia (29.5%), acute pancreatitis (16.4%), exacerbations of COPD and CNS non-infections (both 13.1%). At HTD common diagnoses were: tetanus (63.2%), CNS infections (16.4%), and sepsis (7.2%). Pneumonia was common at NHTD and BMH, accounting for about 30% of patients, while it was just 4.6% at HTD. (Table 5 - 3).

Table 5 - 3. Admission diagnosis by study site

Admission diagnosis	Total, n (%)	NHTD, n (%)	BMH, n (%)	HTD, n (%)
Tetanus	132 (35.3)	36 (22.4)	0	96 (63.2)
Pneumonia	73 (19.5)	48 (29.8)	18 (29.5)	7 (4.6)
CNS infections	60 (16.0)	34 (21.1)	1 (1.6)	25 (16.4)
Septic shock	28 (7.5)	26 (16.1)	2 (3.3)	0
Sepsis	27 (7.2)	12 (7.5)	4 (6.6)	11 (7.2)
CNS non-infections	14 (3.7)	4 (2.5)	8 (13.1)	2 (1.3)
Acute pancreatitis	10 (2.7)	0	10 (16.4)	0
COPD	9 (2.4)	0	8 (13.1)	1 (0.7)
Dengue	9 (2.4)	0	0	9 (5.9)
Other illnesses	12 (3.2)	1 (0.6)	10 (16.4)	1 (0.7)
Total	374 (100.0)	161 (100.0)	61 (100.0)	152 (100.0)

CNS non-infections: 4 post brain operation, 3 coma/diabetes mellitus, 3 brain hemorrhage, 2 hepatic comas, 1 epilepsy, 1 spiral cord compression.
Other illnesses: 3 myocardiac infarction, 2 acute renal failures, and 1 post cardiac valve replacement operation, 1 hepatic abscess, 1 malaria, and 1 unknown original fever, 1 after cardiac arrest, 1 pulmonary artery thrombosis, 1 chest trauma with atelectasis.

5.3.2.5 Characteristics of patients according to admission diagnosis

The median APACHE II score at ICU admission ranged from 6 to 16 points between admission diagnoses. Low medians were seen in tetanus patients (6 points) and acute pancreatitis (9 points), the median of the other diagnoses were 12 points or higher with the highest was seen in COPD (16 points). The median age ranged widely from 27 years in dengue patients to 66 years in COPD patients. Male gender accounted for more than 50% in most diagnoses, except in dengue where this was lower: 33.3%. The proportion of patients with a comorbidity ranged from 9.1% in tetanus up to 90% in acute pancreatitis. Proportion of patients transferred from other hospitals to the study sites were widely different from 22.2% in COPD to 92.9% in septic shock. Antibiotic use was different between admission diagnosis: from 55.6% in dengue up to 100% in acute pancreatitis. For most admission diagnoses under one third of patients had tracheostomy during ICU stay with exception of tetanus and CNS infections, where the proportion having tracheostomy was 100% and 61.0%

respectively. A high proportion of patients used sedatives, ranged from 75.0% in CNS infections to 100% in septic shock, acute pancreatitis, and tetanus. Neuromuscular paralysis was used in 86.4% of tetanus patients but under a quarter of patients with the other diagnoses. Steroid was used most commonly in CNS infections (68.3%), followed by pneumonia (54.8%), and septic shock (53.6%). The proportion of patients that used vasopressors ranged from 11.1% in COPD to 96.4% in septic shock. The median time patients spent on the ventilator ranged from 5 days in dengue up to 14 days in CNS infections, with the highest of 17 days in tetanus. (Table 5 – 4).

Table 5 - 4. Participants' characteristics and treatment according to admission diagnosis

Admission diagnosis	APACHE II, median (IQR)	Age, median (IQR)	Male gender, n (%)	Co-morbidity n (%)	Hospital Transfer, n (%)	Antibiotic on ICU admission, n (%)	Trache-ostomy, n (%)	Sedative, n (%)	Neuro-muscular paralysis, n (%)	Steroid, n (%)	Vaso-pressor, n (%)	Ventilation days, median (IQR)
Tetanus, n = 132	6 (3 – 8)	52 (41 – 67.5)	103 (78.0)	12 (9.1)	107 (81.1)	121 (91.7)	132 (100)	132 (100)	114 (86.4)	6 (4.5)	17 (12.9)	17.5 (13 – 24)
Pneumonia, n = 73	12 (8 – 17)	57 (42 – 73.5)	51 (69.9)	47 (64.4)	52 (71.2)	65 (89.0)	25 (34.2)	68 (93.2)	16 (21.9)	40 (54.8)	35 (47.9)	9 (6 – 15.5)
CNS infections, n = 60	12 (10 – 16)	47.5 (30.5– 56.8)	42 (70.0)	18 (30.0)	52 (86.7)	44 (73.3)	37 (61.7)	45 (75.0)	6 (10.0)	41 (68.3)	14 (23.3)	14 (7.3 – 33)
Septic shock, n=28	14 (10.8 – 19)	51.5 (46 – 61.8)	21 (75.0)	22 (78.6)	26 (92.9)	26 (92.9)	8 (28.6)	28 (100.0)	7 (25.0)	15 (53.6)	27 (96.4)	11.5 (7 – 16)
Sepsis, n = 27	14 (10 – 17)	50 (35 – 66)	16 (59.3)	12 (46.2)	22 (81.5)	23 (85.2)	4 (14.8)	24 (92.3)	6 (23.1)	12 (46.2)	19 (73.1)	6 (5 – 9)
CNS non-infections, n= 14	14 (11.8– 19.8)	57 (25.8 – 65)	8 (57.1)	9 (64.3)	7 (50.0)	10 (71.4)	4 (28.6)	13 (92.9)	1 (7.1)	4 (28.6)	3 (21.4)	6 (4.8 – 9.8)
Acute pancreatitis, n = 10	9 (5.8 – 12.3)	49 (40.5– 66.3)	9 (90)	9 (90.0)	3 (30.0)	10 (100)	1 (10.0)	10 (100)	0	0	3 (30.0)	6 (4.8 – 9.8)
COPD, n = 9	16 (15 – 17)	66 (50 – 75.5)	8 (88.9)	8 (88.9)	2 (22.2)	8 (88.9)	2 (22.2)	8 (88.9)	1 (11.1)	3 (33.3)	1 (11.1)	6 (4.5 – 15)
Dengue, n = 9	14 (9.5 – 16)	27 (19.5– 34.5)	3 (33.3)	1 (11.1)	6 (66.7)	5 (55.6)	0	8 (88.9)	1 (11.1)	3 (33.3)	7 (77.8)	5 (4 - 10
Other illnesses, n = 12	11 (10 – 16.5)	54 (39 – 63.8)	6 (50.0)	6 (50.0)	4 (33.3)	11 (91.7)	0	10 (83.3)	0	3 (25.0)	4 (33.3)	7 (4 – 9.3)
Total, n = 374	10 (6 – 15)	52 (38 – 64)	267 (71.4)	144 (38.7)	281 (75.1)	323 (86.4)	213 (57.0)	346 (93.0)	152 (40.9)	127 (34.1)	130 (34.9)	12 (6 – 22)

Tetanus patients accounted for almost one third of study patients and high requirement for neuromuscular blocking-agent paralysis. Therefore, analysis was carried out separately. All factors except for age and proportion transferred from other hospitals outlined earlier (demographic characteristics, comorbidities and factors before ICU admission) were statistically different between tetanus and non-tetanus patients (Table 5 – 5, Table 5 – 6, and Table 5 – 7). Though given the large number of factors tested, the significance of some of the observed variation such as in sex, immune deficiency and transfer from another hospital, should be considered with caution. Nevertheless due to the very distinct differences in pathology and treatment between tetanus patients and other patients analyses have been performed separately and as a whole group.

Table 5 – 5. Demographic characteristics of tetanus and non-tetanus patients

Risk factors		**Non-tetanus, n = 242**	**Tetanus, n = 132**	**P[a] value**
SOFA, median (IQR), mean ± SD		6 (4 – 9), 6.8 ± 3.8	2 (1 – 3), 2 ± 1.5	< 0.0005[b]
APACHE II, median (IQR), mean ± SD		13 (10 – 17), 13.4 ± 5.3	6 (3 – 8), 6.3 ± 4.2	< 0.0005[b]
Age (years), median (IQR), mean ± SD		51 (37 – 63.3), 50.7 ± 18.0	52 (41 – 67.5), 53.9 ± 18.1	0.202[b]
Age (years)	> 60 <= 60	75 (31.0%) 167 (69.0%)	44 (33.3%) 88 (66.7%)	0.644
Gender	Male Female	164 (67.8%) 78 (32.2%)	103 (78.0%) 29 (22.0%)	0.042
Comorbidity	Yes No	132 (55.0%) 108 (45.0%)	12 (9.1%) 120 (90.9%)	< 0.0005
Alcoholic addiction	Yes No	54 (22.3%) 188 (77.7%)	2 (1.5%) 130 (98.5%)	< 0.0005
Diabetes mellitus	Yes No	34 (14.0%) 208 (86.0%)	1 (0.8%) 131 (99.2%)	< 0.0005
Chronic lung disease	Yes No	21 (8.7%) 220 (91.3%)	2 (1.5%) 130 (98.5%)	0.006
Immunity deficiency	Yes No	14 (5.8%) 228 (94.2%)	1 (0.8%) 131 (99.2%)	0.024
Cirrhosis	Yes No	11 (4.5%) 231 (95.5%)	0 132	0.010

[a] Fisher's Exact Test unless otherwise stated, [b] Mann Whitney and Median Test. Missing: Non-tetanus SOFA 26, APACHE II 23; tetanus SOFA 18, APACHE II 10.

Table 5 – 6. Medical factors before and at ICU admission of tetanus and non-tetanus patients

Factors		Non-tetanus, n = 242	Tetanus, n = 132	P value[a]
Inpatient in past 90 days	Yes	36 (14.9%)	5 (3.8%)	0.001
	No	206 (85.1%)	127 (96.2%)	
Antibiotic use in past 90 days	Yes	22 (9.1%)	3 (2.3%)	0.015
	No	220 (90.9%)	129 (97.7%)	
Transfer from another hospital	Yes	174 (71.9%)	107 (81.1%)	0.060
	No	68 (28.1%)	25 (18.9%)	
Intubation before admission	Yes	40 (16.5%)	5 (3.8%)	< 0.0005
	No	202 (83.5%)	127 (96.2%)	
AB in this illness on ICU admission	Yes	202 (83.5%)	121 (91.7%)	0.028
	No	40 (16.5%)	11 (8.3%)	

[a] Fisher's Exact Test

Table 5 – 7. Treatment for tetanus and non-tetanus patients

Treatment		Non-tetanus, n = 242	Tetanus, n = 132	P[a] value
Sedatives	Yes	214 (89.2%)	132 (100%)	< 0.0005
	No	26 (10.8%)	0	
Neuromuscular paralysis	Yes	38 (15.8%)	114 (86.4%)	< 0.0005
	No	202 (84.2%)	18 (13.6%)	
Proton pump inhibitor	Yes	206 (86.2%)	51 (38.6%)	< 0.0005
	No	33 (13.8%)	81 (61.4%)	
Insulin	Yes	83 (34.6%)	12 (9.1%)	< 0.0005
	No	157 (65.4%)	120 (90.9%)	
Steroids	Yes	121 (50.4%)	6 (4.5%)	< 0.0005
	No	119 (49.4%)	126 (95.5%)	
Vasopressor	Yes	113 (47.1%)	17 (12.9%)	< 0.0005
	No	127 (52.9%)	115 (87.1%)	
Hemodialysis	Yes	50 (20.7%)	9 (6.8%)	< 0.0005
	No	191 (79.3%)	123 (93.2%)	
Transfusion	Yes	76 (31.8%)	9 (6.9%)	< 0.0005
	No	163 (68.2%)	122 (93.1%)	
Tracheostomy	Yes	81 (33.9%)	132 (100%)	< 0.0005
	No	158 (66.1%)	0	
Thoracentesis	Yes	26 (11.0%)	0	< 0.0005
	No	210 (89.0%)	132 (100%)	
Days on ventilator, median (IQR), mean ± SD		8.5 (5 – 16), 14.3 ± 15.7	17.5 (13 – 24), 20.2 ± 14.0	< 0.0005[b]
Days in ICU, median (IQR), mean ± SD		14 (9 – 27), 21.5 ± 20.2	26 (20 – 35), 29.1 ± 16.0	< 0.0005[b]

[a] Fisher's Exact Test unless otherwise stated, [b] Mann Whitney and Median Test

5.3.3 Ventilator-associated pneumonia (VAP) and ventilator-associated respiratory infections (VARI)

5.3.3.1 VAP and VARI incidence

In the study period, a total of 37/374 (9.9%) patients developed VAP. The VAP incidence in the 28 day follow up of the study period at NHTD, BMH, and HTD were 7.5%, 13.1%, and 11.2% respectively. Time from beginning of ventilation to developing VAP ranged from 3 to 26 days with a median (IQR) time of 10 (5.5 – 12) days (Table 5 - 8, Table 5 - 9). There were two patients with VAT presentation who then developed VAP after one and two weeks, both patients were treated with colistin and an anti-Pseudomonal carbapenem initially.

Besides these VAP episodes, there were 55 other ventilator-associated respiratory infections (VARI), which included ventilator-associated pneumonia not fulfilling VAP criteria and ventilator-associated tracheobronchitis [See Chapter 2 section 2.3.4]. In total, there were 92 VARI patients making the VARI incidence of 24.6% (92/374) in the study time follow up. There was no significantly difference in rates between study sites. (Table 5 – 8).

The incidence density of VAP and VARI was 7.6 and 21.4 episodes per 1000 ventilation days respectively (Table 5 - 8). The incidence density of VAP per 1000 ventilation days was the highest at BMH (15.8 episodes) then HTD (8.1 episodes), and lowest at NHTD (5.2 episodes). The incidence density was statistically significant between NHTD and BMH ($p = 0.036$), though in the light of the other findings and the number of tests performed this may still be a chance finding. There was no statistically significant difference in VARI incidence density between the three sites. (Table 5 - 8).

In total, mean (95% CI) and median (IQR) time for developing VARI from beginning of ventilation was 10.4 (9.2 – 11.6) days and 10 (6 – 14) days, respectively. Median time from beginning of ventilation to develop VAP and VARI was 10 days and 9 days, respectively, and this difference was not statistically significant ($p = 0.752$) (Table 5 - 9).

Table 5 - 8. Incidence & incidence density of VAP and VARI by Study Site

VARI events	Total (n=374)	NHTD (n=161)	BMH (n=61)	HTD (n=152)	P value[1]	P value[2]	P value[3]
VAP, n (%)	37 (9.9%)	12 (7.5%)	8 (13.1%)	17 (11.2%)	0.197	0.330	0.814
Other VARI, n (%)	55 (14.7%)	27 (16.0%)	5 (8.2%)	23 (15.1%)	0.183	0.826	0.290
Total VARI, n (%)	92 (24.6%)	39 (24.2%)	13 (21.3%)	40 (26.3%)	0.725	0.698	0.488
VAP incidence (episodes/1000 VD)	7.6 (37/4893)	5.2 (12/2286)	15.8 (8/507)	8.1 (17/2100)	0.036	0.330	0.190
VARI incidence (episodes/1000 VD)	21.4 (92/4304)	19.4 (39/2009)	28.3 (13/460)	21.8 (40/1835)	0.311	0.683	0.503

[1] NHTD and BMH, [2] NHTD and HTD, and [3] BMH and HTD (All Fisher's Exact Test).
VD: ventilation days.

Table 5 - 9. Time from initiation of ventilation to development of VAP or VARI

Ventilator-associated events	Ventilation time to evolving VAP/VARI (days)		
	Mean (95% CI)	Median (IQR)	Min – max
VAP (n = 37)	10.0 (8.3 – 11.7)	10.0 (5.5 – 12.0)[a]	3.0 – 26.0
VARI excluding VAP (n = 55)	10.7 (9.0 – 12.4)	9 (6.0 – 15.0)[a]	2.0 - 27.0
Total VARI (n = 92)	10.4 (9.2 – 11.6)	10 (6.0 -14.0)	2.0 – 27.0

[a] p = 0.752, Mann Whitney U Test

5.3.3.2. Risk factors for VARI

Patient characteristics

Due to the limited number of VAP cases and the shared aetiological pathway [37], risk factors for VARI as a whole rather than VAP were examined. Only the difference in the APACHE II score was statistically significant between patients with and without VARI (p = 0.022). (Table 5 - 10).

Table 5 - 10. Severity score, age and ventilation days at risk and VARI status

Risk Factors	Non-VARI		VARI		P value[a]
	N	Median (IQR)	N	Median (IQR)	
SOFA score	247	4 (3 – 7)	83	3 (2 – 6)	0.078
APACHE II score	255	11 (7 -15)	86	8.5 (5 – 14)	0.022
Age (years)	282	53 (39.8 – 65)	92	48 (36 – 61.8)	0.218
Ventilation days at risk	282	9 (6 – 16)	92	10 (6 – 14)	0.470

[a] Mann Whitney test

There were no differences in demographic factors between patients with and without VARI. (Table 5 - 11).

Table 5 - 11. Impact of demographics and comorbidities on VARI

Characteristics		**Total**	**Non-VARI**	**VARI patients**		**P value[a]**
			N (%)	**n (%)**	**OR (95% CI)**	
Age (years)	> 60	119	95 (79.8)	24 (20.2)	0.70 (0.41 – 1.18)	0.175
	<= 60	255	187 (73.3)	68 (26.7)	Reference	
Gender	Male	267	197 (73.8)	70 (26.2)	1.37 (0.80 – 2.36)	0.252
	Female	107	85 (79.4)	22 (20.6)	Reference	
Comorbidity	Yes	144	118 (81.9)	26 (18.1)	0.68 (0.38 – 1.19)	0.173
	No	228	162 (71.1)	66 (28.9)	Reference	
Alcoholic addiction	Yes	56	43 (76.8)	13 (23.2)	0.92 (0.47 – 1.79)	0.794
	No	318	239 (75.2)	79 (24.8)	Reference	
Diabetes mellitus	Yes	35	28 (80.0)	7 (20.0)	0.75 (0.32 – 1.77)	0.508
	No	339	254 (74.9)	84 (25.1)	Reference	
Chronic lung disease	Yes	23	20 (87.0)	3 (13.0)	0.44 (0.13 – 1.52)	0.193
	No	350	261 (74.6)	89 (25.4)	Reference	
Study sites	HTD	152	112 (73.7)	40 (26.3)	1.12 (0.67 – 1.86)	0.670
	BMH	61	48 (78.7)	13 (21.3)	0.85 (0.42 – 1.73)	0.648
	NHTD	161	122 (75.8)	39 (24.2)	Reference	

[a] Univariate logistic regression

Medical factors before and on ICU admission

Antibiotic use and hospital admission in the previous 90 days, transfer from another hospital, and intubation prior to admission to study ICU, and antibiotic use on ICU admission were also investigated for VARI risk. None of these factors was associated with a statistically significant difference in VARI incidence. (Table 5 - 12).

Table 5 - 12. Effects of medical factors before and on ICU admission on VARI

Risk factors		Total, n	No VARI, n (%)	VARI, n (%)	OR (95% CI)	P value[a]
Inpatient in previous 90 days	Yes	41	34 (82.9)	7 (17.1)	0.60 (0.26 – 1.41)	0.240
	No	333	248 (74.5)	85 (25.5)	Reference	
Antibiotic use in 90 days	Yes	25	21 (84.0)	4 (16.0)	0.57 (0.19 – 1.69)	0.307
	No	349	261 (74.8)	88 (25.2)	Reference	
Transfer from another hospital	Yes	281	212 (75.4)	69 (24.6)	0.99 (0.58 – 1.71)	0.973
	No	93	70 (75.3)	23 (24.7)	Reference	
Type of previous hospital	Tertiary	59	44 (74.6)	15 (25.4)	1.05 (0.44 – 2.52)	0.911
	Province	173	130 (75.1)	43 (24.9)	1.02 (0.49 – 2.13)	0.958
	District	49	37 (75.5)	12 (24.5)	Reference	
Intubation before admission	Yes	45	35 (77.8)	10 (22.2)	0.86 (0.41 – 1.81)	0.693
	No	329	247 (75.1)	82 (24.9)	Reference	
Antibiotic use on ICU admission	Yes	323	245 (75.9)	78 (24.1)	0.84 (0.43 – 1.64)	0.611
	No	51	37 (72.5)	14 (27.5)	Reference	

[a] Univariate logistic regression

Admission diagnosis and VARI incidence

Risks for VARI were statistically significant different between admission diagnoses. Patients with septic shock, tetanus, and acute pancreatitis patients had statistically higher risk of VARI than pneumonia patients with odds ratio of 4.47, 5.39, and 6.29 respectively. (Table 5 - 13)

Table 5 - 13. Admission diagnosis and VARI

Diagnosis	Total, n	No VARI, n (%)	VARI, n (%)	OR (95% CI)	P value[a]
Septic shock	28	19 (67.9)	9 (32.1)	4.47 (1.47 – 13.58)	0.008
Tetanus	132	84 (63.6)	48 (36.4)	5.39 (2.29 – 12.68)	< 0.0005
Acute pancreatitis	10	6 (60.0)	4 (40.0)	6.29 (1.42 – 27.77)	0.015
Chronic obstructive pulmonary diseases	9	6 (66.7)	3 (33.3)	4.71 (0.96 – 23.12)	0.056
CNS infections	60	49 (81.7)	11 (18.3)	2.12 (0.77 – 5.85)	0.149
Other illnesses	12	9 (75.0)	3 (25.0)	3.14 (0.69 – 14.39)	0.140
Sepsis	27	25 (92.6)	2 (7.4)	0.75 (0.15 – 3.88)	0.736
CNS non-infections	14	12 (85.7)	2 (14.3)	1.57 (0.29 – 8.50)	0.600
Dengue	9	6 (66.7)	3 (33.3)	4.71 (0.96 – 23.12)	0.056
Pneumonia	73	66 (90.4)	7 (9.6)	Reference	
Total patients, n (%)	374	282 (75.4)	92 (24.6)		

[a] Univariate logistic regression

CNS non-infections: 4 post brain operation, 3 coma/diabetes mellitus, 3 brain hemorrhage, 2 hepatic comas, 1 epilepsy, 1 spiral cord compression. Other illnesses: 3 myocardiac infarction, 2 acute renal failures, and 1 post cardiac valve replacement operation, 1 hepatic abscess, 1 malaria, and 1 unknown original fever, 1 after cardiac arrest, 1 pulmonary artery thrombosis, 1 chest trauma with atelectasis.

Treatment and VARI incidence

Patients using steroids, had a lower incidence of VARI with an odds ratio of 0.58 (95% CI 0.34 – 0.98; p = 0.042). Other treatments associated with a significant higher incidence of VARI were: neuromuscular paralysis (odds ratio 2,9; 95% CI 1.78-4.72) and tracheostomy (odds ratio 1.74; 95% CI1.08 – 2.82) (Table 5 - 14). These differences in risk were thought to be possibly due to difference in primary diagnosis and therefore further analysis was conducted, comparing risk factors in tetanus and non-tetanus patients (section 5.3.3.3).

Table 5 - 14. Treatments prescribed and VARI

Treatment		Total, n	No VARI, n (%)	VARI, n (%)	OR (95% CI)	P value[a]
Sedatives	Yes	346	257 (74.3)	89 (25.7)	4.16 (0.96 – 17.94)	0.056
	No	26	24 (92.3)	2 (7.7)	Reference	
Neuromuscular paralysis	Yes	152	97 (63.8)	55 (36.2)	2.90 (1.78 – 4.72)	< 0.0005
	No	220	184 (83.6)	36 (16.4)	Reference	
Proton pump inhibitors	Yes	257	196 (76.3)	61 (23.7)	0.87 (0.53 – 1.45)	0.594
	No	114	84 (73.7)	30 (26.3)	Reference	
Insulin	Yes	95	73 (76.8)	22 (23.2)	0.91 (0.53 – 1.57)	0.732
	No	277	208 (75.1)	69 (24.9)	Reference	
Steroids	Yes	127	104 (81.9)	23 (18.1)	0.58 (0.34 – 0.98)	0.042
	No	245	177 (72.2)	68 (27.8)	Reference	
Vasopressor	Yes	130	95 (73.1)	35 (26.9)	1.22 (0.75 – 2.00)	0.419
	No	242	186 (76.9)	56 (23.1)	Reference	
Hemodialysis	Yes	59	42 (71.2)	17 (28.8)	1.29 (0.69 – 2.40)	0.421
	No	314	239 (76.1)	75 (23.9)	Reference	
Transfusion	Yes	85	63 (74.1)	22 (25.9)	1.11 (0.64 – 1.94)	0.703
	No	285	217 (76.1)	68 (23.9)	Reference	
Tracheostomy[b]	Yes	189	133 (70.4)	56 (29.6)	1.74 (1.08 – 2.82)	0.023
	No	185	149 (80.5)	36 (19.5)	Reference	
Thoracentesis	Yes	26	17 (65.4)	9 (34.6)	1.70 (0.73 – 3.96)	0.219
	No	341	260 (76.2)	81 (23.8)	Reference	

[a] Univariate logistic regression
[b] Tracheostomy considered as a risk factor for VARI only if performed at least 2 days before VARI developed.

5.3.3.3 Risk factor for VAP/VARI in non-tetanus and tetanus patients

In this study, tetanus patients were the largest number (132 patients), accounting for more than one third of the study population (35.3%) and nearly double the number of pneumonia

patients (73 patients), the second largest number of patients divided by admission diagnosis. Severe tetanus patients are commonly considerably different to patients with other admission diagnoses in terms of the time on mechanical ventilation, lower age and less comorbidities (Table 5-4). Patients require supportive treatment and uniquely long periods of muscle relaxant and high sedation compared to other patient groups. In addition the underlying disease process is often seen as an isolated dysfunction of the musculoskeletal system rather than a multisystem disorder such as sepsis. Because of these differences between tetanus patients and the other patients, tetanus and non-tetanus patients were separately analysised to find risk factors for VARI.

VARI incidence between non-tetanus and tetanus patients

VAP incidence in tetanus patients (10.5%) was higher as compared to non-tetanus patients (9.5%), with incidence density of VAP per 1000 ventilation days at risk in tetanus patients of 6.4 episodes versus 8.5 episodes in non-tetanus patients ($p = 0.499$, Table 5 - 15). In contrast, other VARI (without VAP) and total VARI incidence, and incidence density in tetanus patients were higher than in non-tetanus patients. In univariate logistic regression, tetanus patients had increased risk of VARI with an OR of 2.53 (95% CI 1.56 – 4.09) compared to non-tetanus patients ($p < 0.0005$) (Table 5 - 15).

SOFA, APACHE II score and ventilation days at risk in non-tetanus and tetanus patients

There was no significant difference in age, SOFA score and APACHE II score between VARI and non-VARI patients in both tetanus and non-tetanus group. In non-tetanus patients, the median ventilation days at risk (days on ventilator while patients in current ICU without VARI) in VARI patients (10.5 days) was longer than that (7 days) in non-VARI patients, but this difference did not reach statistical significance ($p=0.089$). Whereas, in tetanus group the median ventilation days at risk in VARI patients (8.5 days) was statistically significantly different from that in non-VARI patients (15 days, $p < 0.001$). (Table 5 - 16)

Impact of Demographics on VARI in non-tetanus and tetanus patients

There was no significant difference in VARI incidence between gender, age group, or having a comorbidity when analysed by non-tetanus and tetanus groups. In the non-tetanus group, the VARI incidence was not significantly different between the study sites. In the tetanus group, VARI incidence at HTD (31.2%) was lower than at NHTD (50%) with OR (95% CI) 0.46 (0.21 – 0.995) and p = 0.048. (Table 5 - 17).

Medical factors before and on ICU admission

Patients with history of hospital admission and antibiotic use in past 90 days, transfer from other hospital to the study sites, type of transfer hospitals, intubation before admission, and antibiotics use at ICU admission had no significant differences in VARI incidence in comparison with patients without these in both non-tetanus and tetanus group. (Table 5 - 18).

Treatment and VARI incidence in non-tetanus and tetanus patients

In non-tetanus patients, thoracocentesis was the only factor significantly associated with increased risk for VARI with odds ratio of 2.74 (95% CI 1.13 – 6.66). In tetanus patients, only vasopressor use was significantly associated with a higher VARI incidence compared to those not using vasopressors, (odds ratio 2.90, 95% CI 1.02 – 8.20). The statistically significant effect of steroid use and tracheostomy for VARI incidence overall were not seen when in both non-tetanus and tetanus patients separately. (Table 5 - 19) It should be noted that only 6 patients with tetanus were treated with steroids.

Table 5 - 15. VAP/VARI incidence and incidence density among non-tetanus and tetanus patients at each site

VARI	Non-Tetanus				Tetanus				P value[1]
	NHTD (n = 125)	**BMH (n = 61)**	**HTD (n = 56)**	**Total** (n = 242)	**NHTD (n = 36)**	**BMH (n = 0)**	**HTD (n = 96)**	**Total (n = 132)**	
VAP, n (%)	9 (7.2%)	8 (13.1%)	6 (10.7%)	23 (9.5%)	3 (8.3%)		11 (11.5%)	14 (10.6%)	0.894
Other VARI, n (%)	12 (9.6%)	5 (8.2%)	4 (7.1%)	21 (8.7%)	15 (41.7%)		19 (19.8%)	34 (25.8%)	< 0.0005
Total VARI[a], n (%)	21 (16.8%)	13 (21.3%)	10 (17.9%)	44 (18.2%)[a]	18 (50%)		30 (31.2%)	48 (36.4%)[a]	0.0016
VAP incidence (episodes/1000 VD)	5.6	15.8	9.8	8.5	4.3		7.4	6.4	0.4999
VARI incidence (episodes/1000 VD)	13.9	28.3	18.2	17.5	35.9		23.3	26.9	0.0433

[1] comparison tetanus and non-tetanus patients in total (Fisher's Exact Test). [a] OR (95% CI) of total VARI incidence in tetanus and non-tetanus was 2.53 (1.56 – 4.09) p < 0.0005 (univariate logistic regression). VD: ventilation days.

Table 5 - 16. SOFA, APACHE II score, ventilation day at risk and VARI status

Risk factors	Non-Tetanus					Tetanus				
	No VARI		VARI		P value[a]	No VARI		VARI		P value[a]
	N	Median (IQR),	N	Median (IQR),		N	Median (IQR),	N	Median (IQR),	
Age (years)	198	52 (37 – 64),	44	48 (32 – 62.3),	0.259	84	54 (41.5 – 68),	48	49 (41 – 61.8),	0.333
SOFA score	176	6 (3 – 9),	40	6.5 (5 – 11),	0.136	71	2 (1 – 3),	43	2 (1 – 3),	0.998
APACHE II score	177	13 (10 – 17),	42	13 (10 – 17.3),	0.484	78	7 (3 – 9),	44	5 (2.3 – 7.8),	0.089
Ventilation days at risk[c]	198	7.5 (5 – 13),	44	10.5 (6 – 14)[b],	0.092	84	15 (10 – 21.3),	48	8.5 (6 – 14.5)[b],	< 0.0005

[a] Mann Whitney U Test, [b] Ventilation days at risk for VARI between tetanus and non-tetanus patients was not statistically significant difference with p = 0.445[a], [c] days on ventilator while patients in current ICU without VARI.

Table 5 - 17. Comparison of demographics in patients with and without VARI by tetanus status

Characteristics		Non-tetanus					Tetanus				
Risk factors		**Total, n**	**No VARI, n (%)**	**VARI, n (%)**	**OR (95% CI)**	**P value[a]**	**Total, n**	**No VARI, n (%)**	**VARI, n (%)**	**OR (95% CI)**	**P value[a]**
Age (years)	> 60	75	64 (85.3)	11 (14.7)	0.70 (0.33 – 1.47)	0.344	44	31 (70.5)	13 (29.5)	0.64 (0.29 – 1.40)	0.251
	<= 60	167	134 (80.2)	33 (19.8)	Reference		88	53 (60.2)	35 (39.8)	Reference	
Gender	Male	164	135 (82.3)	29 (17.7)	0.90 (0.45 – 1.80)	0.771	103	62 (60.2)	41 (39.8)	2.08 (0.81 – 5.31)	0.126
	Female	78	63 (80.8)	15 (19.2)	Reference		29	22 (75.9)	7 (24.1)	Reference	
Comorbidity	Yes	132	109 (82.6)	23 (17.4)	0.87 (0.45 – 1.68)	0.688	12	9 (75.0)	3 (25.0)	0.56 (0.14 – 2.16)	0.396
	No	108	87 (80.6)	21 (19.4)	Reference		120	75 (62.5)	45 (37.5)	Reference	
Alcoholic addiction	Yes	54	42 (77.8)	12 (22.2)	1.39 (0.66 – 2.94)	0.384	2	1 (50.0)	1 (50.0)	1.77 (0.11 – 28.89)	0.690
	No	188	156 (83.0)	32 (17.0)	Reference		130	83 (63.8)	47 (36.2)	Reference	
Diabetes mellitus	Yes	34	27 (79.4)	7 (20.6)	1.20 (0.49 – 2.96)	0.695	1	1 (100.0)	0	0.000	1.000
	No	208	171 (82.2)	37 (17.8)	Reference		131	83 (63.4)	48 (36.6)	Reference	
Chronic lung disease	Yes	21	18 (85.7)	3 (14.3)	0.73 (0.21 – 2.59)	0.623	2	2 (100.0)	0	0.000	0.999
	No	220	179 (81.4)	41 (18.6)	Reference		130	82 (63.1)	48 (36.9)	Reference	
Study sites	HTD	56	46 (82.1)	10 (17.9)	1.08 (0.47 – 2.47)	0.821	96	66 (68.8)	30 (31.2)	0.46 (0.21 – 0.995)	0.048
	BMH	61	48 (78.7)	13 (21.3)	1.34 (0.62 – 2.90)	0.456	0				
	NHTD	125	104 (83.2)	21 (16.8)	Reference		36	18 (50.0)	18 (50.0)	Reference	

[a] Univariate logistic regression

Table 5 - 18. Univariate analysis of relationship between interventions before ICU admission and VARI

Risk factors		Non-Tetanus					Tetanus				
		Total (n)	No VARI, n (%)	VARI n (%)	OR (95% CI)	P value[a]	Total (n)	No VARI, n (%)	VARI, n (%)	OR (95% CI)	P value[a]
Inpatient 90 days prior	Yes	36	31 (86.1)	5 (13.9)	0.69 (0.25 – 1.89)	0.471	5	3 (60.0)	2 (40.0)	1.17 (0.19 – 7.28)	0.863
	No	206	167 (81.1)	39 (18.9)	Reference		127	81 (63.8)	46 (36.2)	Reference	
Antibiotic use in 90 days	Yes	22	19 (86.4)	3 (13.6)	0.69 (0.20 – 2.44)	0.564	3	2 (66.6)	1 (33.3)	0.87 (0.08 – 9.88)	0.912
	No	220	179 (81.4)	41 (18.6)	Reference		129	82 (63.6)	47 (36.4)	Reference	
Transfer from another hospital	Yes	174	143 (82.2)	31 (17.8)	0.92 (0.45 – 1.88)	0.813	107	69 (64.5)	38 (35.5)	0.83 (0.34 – 2.02)	0.779
	No	68	55 (80.9)	13 (19.1)	Reference		25	15 (60.0)	10 (40.0)	Reference	
Referral hospital type	Tertiary	53	41 (77.4)	12 (22.6)	1.23 (0.38 – 3.95)	0.729	6	3 (50.0)	3 (50.0)	2.29 (0.37 – 14.25)	0.376
	Province	96	81 (84.4)	15 (15.6)	0.78 (0.25 – 2.38)	0.660	77	49 (63.6)	28 (36.4)	1.31 (0.48 – 3.56)	0.601
	District	26	21 (80.8)	5 (19.2)	Reference		23	16 (69.6)	7 (30.4)	Reference	
Intubation before admission	Yes	40	31 (77.5)	9 (22.5)	1.39 (0.61 – 3.17)	0.440	5	4 (80.0)	1 (20.0)	0.43 (0.05 – 3.92)	0.451
	No	202	167 (82.7)	35 (17.3)	Reference		127	80 (63.0)	47 (37.0)	Reference	
AB in this illness on ICU admission	Yes	202	167 (82.7)	35 (17.3)	0.72 (0.32 – 1.65)	0.440	121	78 (64.5)	43 (35.5)	0.66 (0.19 – 2.30)	0.515
	No	40	31 (77.5)	9 (22.5)	Reference		11	6 (54.5)	5 (45.5)	Reference	

[a] Univariate logistic regression

Table 5 - 19. Treatments prescribed and VARI in non-tetanus and tetanus patients

Treatment		Non-Tetanus					Tetanus				
		Total, n	No VARI, n (%)	VARI, n (%)	OR (95% CI)	P value[a]	Total, n	No VARI, n (%)	VARI, n (%)	OR (95% CI)	P value[a]
Sedatives	Yes	214	173 (80.8)	41 (19.2)	2.84 (0.65 – 12.52)	0.167	132	84 (63.6)	48 (36.4)		
	No	26	24 (92.3)	2 (7.7)	Reference		0	0	0		
Neuromuscular paralysis	Yes	38	27 (71.1)	11 (28.9)	2.16 (0.98 – 4.80)	0.057	114	70 (61.4)	44 (38.6)	2.20 (0.68 – 7.11)	0.188
	No	202	170 (84.2)	32 (15.8)	Reference		18	14 (77.8)	4 (22.2)	Reference	
Proton pump inhibitor	Yes	206	167 (81.1)	39 (18.9)	1.69 (0.56 – 5.10)	0.349	51	29 (56.9)	22 (43.1)	1.61 (0.78 – 3.31)	0.201
	No	33	29 (87.9)	4 (12.1)	Reference		81	55 (67.9)	26 (31.1)	Reference	
Insulin	Yes	83	65 (78.3)	18 (21.7)	1.46 (0.75 – 2.87)	0.270	12	8 (66.7)	4 (33.3)	0.86 (0.25 – 3.03)	0.819
	No	157	132 (84.1)	25 (15.9)	Reference		120	76 (63.3)	44 (36.7)	Reference	
Steroids	Yes	121	100 (82.6)	21 (17.4)	0.93 (0.48 – 1.79)	0.819	6	4 (66.7)	2 (33.3)	0.87 (0.15 – 4.93)	0.875
	No	119	97 (81.5)	22 (18.5)	Reference		126	80 (63.5)	46 (36.5)	Reference	
Vasopressor	Yes	113	88 (77.9)	25 (22.1)	1.72 (0.88 – 3.36)	0.111	17	7 (41.2)	10 (58.8)	2.90 (1.02 – 8.20)	0.045
	No	127	109 (85.8)	18 (14.2)	Reference		115	77 (67.0)	38 (33.0)	Reference	
Hemodialysis	Yes	50	38 (76.0)	12 (24.0)	1.57 (0.74 – 3.33)	0.240	9	4 (44.4)	5 (55.6)	2.33 (0.59 – 9.12)	0.226
	No	191	159 (83.2)	32 (16.8)	Reference		123	80 (65.0)	43 (35.0)	Reference	
Transfusion	Yes	76	60 (78.9)	16 (21.1)	1.34 (0.67 – 2.68)	0.401	9	3 (33.3)	6 (66.7)	3.95 (0.94 – 16.61)	0.061
	No	163	136 (83.4)	27 (16.6)	Reference		122	81 (66.4)	41 (33.6)	Reference	
Tracheostomy	Yes	57	49 (86.0)	8 (14.0)	0.68 (0.29 – 1.55)	0.355	132	84 (63.6)	48 (36.4)		
	No	185	149 (80.5)	36 (19.5)	Reference		0	0	0		
Thoracentesis	Yes	26	17 (65.4)	9 (34.6)	2.74 (1.13 – 6.66)	0.026	0	0	0		
	No	210	176 (83.8)	34 (16.2)	Reference		132	84 (63.6)	48 (36.4)		

[a] Univariate logistic regression

5.4 Discussion

This study is the largest study on VAP/VARI in Vietnam, including a general ICU in the largest hospital in Hanoi (BMH) and two ICUs in teaching referral hospitals in Hanoi and Ho Chi Minh city specializing in infectious diseases. The results of this study supply the data to depict a more detailed picture of VAP/VARI in Vietnamese ICUs and play an important part in planning strategies to limit and manage VAP/VARI as well as other HAI in ICUs in Vietnam.

5.4.1 VAP and VARI incidence

Although incidence density is believed to be a better marker of VAP occurrence (correcting for different days at risk), both incidence and incidence density are reported here to be comparable with other studies. In current study, VAP incidence was 9.9% and incidence density was 7.6 episodes per 1000 ventilation days (Table 5 – 8), these are considerably lower than those reported from some previous studies in Vietnamese ICUs. The author, with colleagues, has previously reported VAP incidence of 17.4% and VAP incidence density of 11.7 episodes/1000 ventilation days at NHTD in 2012 [118]. Truong Anh Thu et al. surveyed at Bach Mai Hospital in 2008 – 2009, reporting VAP incidence of 18.9% and VAP incidence density of 27.4 episodes/1000 ventilation days [119]. Recently, a report by Tran Huu Thong et al from a trial to evaluate the efficacy of subglottic tracheal tube suction in comparison with standards tracheal tubes to prevent VAP at Bach Mai Hospital in 2009 – 2013 showed a high VAP incidence, 56.6% and 39.0% in patients intubated with traditional tracheal tube and subglottic tracheal tube respectively [121].

The VAP incidence density in this study is also substantially lower than pooled VAP density of other developing countries, 22.9 episodes/1000 ventilation days in a systematic review by Allegranzi et al in 2011 [10] or 17.2 episodes/1000 ventilation days in an international multicentre study by Rosenthal et al in 2012 [175]. The incidence in this study is even lower

than that in some developed countries, 7.9 episodes/1000 ventilation days as in a report of WHO in 2011 [1].

This difference could be explained largely by the VAP criteria used in these studies. All the other studies used different VAP diagnosis criteria (most of them were CDC criteria for diagnosis VAP in 2008 [2008 CDC criteria] [13]) to that used in this study which is CDC criteria for VAP in 2013 (2013 CDC criteria) [23]. The main difference is that the 2013 criteria require firstly a deterioration in respiratory status after a period of improvement or stability. This initial criterion in the 2013 CDC criteria is intended to identify VAP patients with poor respiratory function, through their need for increased ventilation support (F_iO_2 and PEEP) to achieve adequate oxygenation. Thus deterioration in lung function resulting from lung infection requires an increase in F_iO_2 or PEEP to achieve adequate oxygenation. However, in mechanically ventilated patients with normal premorbid lung function, as seen in many patients with encephalitis and tetanus, it is likely that substantial damage to the lung is required to decrease oxygenation to a level at which there is a need to increase F_iO_2 or PEEP to secure adequate oxygenation. In this situation, treating physicians usually recognize the presence of VAP through infectious symptoms and more subtle decline in lung function, for example patients presenting with fever, increased sputum, decrease in respiratory function demonstrated by a decline in P_aO_2/F_iO_2 ratio. Another reason for potential low sensitivity of the 2013 CDC criteria for recognition of VAP in resource poor settings is the restricted ability to closely monitor arterial oxygen partial pressure and thus tailor ventilator settings to this. For example it is common for Vietnamese physicians have to set F_iO_2 to around 40% to be sure of adequate oxygenation in as patients who are only monitored with pulse oximetry. Furthermore old ventilators with inaccurate flow and pressure metres are also set conservatively to ensure patient safety in a setting with limited monitoring capacity and low nurse : patient ratios. Consequently, in patients with normal lung function if VAP were to develop, it would take a large reduction in P_aO_2 to bring oxygen saturations to a level that would need a change in F_iO_2 or PEEP and meet the 2013 CDC criteria. In clinical practice,

physicians commonly recognize this situation early and carry out diagnostic procedures and give empiric antibiotic treatment. In our series, VARI incidence and incidence density were similar to reported rates of VAP, and therefore it is possible that many of these patients would have met CDC criteria if given Western levels of monitoring and equipment to allow more careful ventilator adjustment. This point was further supported by the finding that the median (IQR) ventilation time in ICU to developed VAP and VARI were almost the same 10 days (Table 5 - 9). In conclusion, it seems likely that many patients that would have been diagnosed with VAP using the older CDC criteria are not recognized by the 2013 CDC criteria. In our study there were 41 patients among 55 'other VARI' patients who were diagnosed with pneumonia by the treating physician. All these patients were treated under name other VARI and none of them progressed to VAP. We did not design to collect chest x-ray data for this phenomenon so we could not determine these patients developed pneumonia or VAT.

Low sensitivity of the 2013 CDC criteria to identify VAP has been found by other studies. Wallace et al found that there was a discrepancy in identify VAP among different systems. VAP incidence (episodes/1000 ventilation days) by CPIS (36.3), HELICS (22.2), 2008 CDC criteria (15.2), and clinical diagnosis (15.2) was much higher VAP incidence found by 2013 CDC criteria (1.1) [177]. Ego et al. used six different systems for VAP identify among 91 patients also found that VAP incidence identified by 2013 CDC criteria (9.9%) was considerable low than CPIS (41.8%) and 2008 CDC criteria (23.1%) [178]. Waltrick et al. used parallel CPIS and 2013 CDC criteria to identify VAP in a prospective observational study at two general ICUs from August 2013 to June 2014 [179]. In this study, there were 168 patients ventilated for > 48 hours in the study period, of which 38 patients were diagnosed VAP by CPIS and 14 patients diagnosed by novel CDC 2013, all these 14 patients included in 38 VAP patients diagnosed by CPIS. Chang et al. used the 2013 CDC criteria retrospectively to identify VAP among 165 conventionally diagnosed VAP patients from April 2010 to February 2014 in five ICUs of regional teaching hospitals in Taiwan [180]. This

study found that just 12.1% (20/165) and 1.2% (2/165) of patients diagnosed VAP by the conventional VAP criteria (combination of clinical, radiology, and microbiology criteria) were diagnosed as possible and probable VAP by 2013 CDC criteria, respectively. Summary main results of these studies are presented in Table 5 – 20.

Table 5 - 20. Summary of results from studies describing differences in VAP incidence depending on criteria used

Author	CPIS	CDC/NSHN PNU1 (2008)	ACCP	New CDC/NHSN (probable VAP)	HELICS	Johanson Criteria	Clinical VAP
Ego et al. [178], % (n)	41.8 (38)	23.1 (21)	17.6 (16)	9.9 (9)	11.0 (10)	4.4 (4)	
Wallace et al. [177], episodes/1000 VD	36.3	15.2		1.1	22.2		15.2
Waltrick et al. [179], % (episodes/1000 VD)	22.6 (13.1)			8.3 (5.2)			

VD: ventilation days

Another reason for this low incidence could be that there was genuinely lower incidence of VAP in our study sites, for example due to infection control improvement in the study hospitals over time. At all study sites over this period the research focus and aim of the hospital management has been to reduce HAI, with VAP being a particular target. Increased knowledge amongst hospital staff and improved awareness of prevention measures may have had a significant effect. In addition daily following patients for VAP and discussion of CDC criteria may have reduced antibiotic prescription and clinical diagnoses of VAP/ VARI. Two previous studies in one of the study site hospitals (BMH) showed a decreased incidence over time, from 34.7 episodes/ 1000 ventilator days in 2002 - 2003 to 27.4 episodes in 2008 - 2009 [116, 119]. Although there was a report showed that VAP incidence density in NHTD in 2012 was 11.7 episodes/1000 ventilation days [118], a decrease of about 4 episodes/1000 ventilation days from 11.7 episodes to 7.6 episodes/1000 ventilation days in one year is hard

to believe because in two previous studies it just decrease 7.3 episodes over 5 year period. This supports more for above hypothesis that new CDC criteria for VAP diagnosis could be less sensitive and miss some VAP cases comparing with old CDC criteria.

5.4.2 Risk factors for VARI

In current study there were significant differences in VARI incidence and incidence density between patients with different admission diagnoses. Septic shock, tetanus, and acute pancreatitis patients had statistically higher risk for VARI than pneumonia patients (Table 5 – 13). This study also found that neuromuscular paralysis use, steroid, and tracheostomy were associated with VARI incidence. However, it is unusual and out of keeping with published studies [3, 181] that steroid use showed protective effect on VARI incidence, whilst tracheostomy resulted in a higher risk for VARI (Table 5 – 14). A further unusual finding was that APACHE II score in VARI patients was statistically lower than non-VARI patient (Table 5 – 10). Whereas Vincent et al. found that patients with higher severity level and immunosuppression had higher rate of infection than patients without these [167]. These counter-intuitive findings were suspected to relate to the high proportion of tetanus patients in our study population. Severe tetanus usually needs ventilation for a long time, about 3 weeks or more on ventilation with further support leading to 4 – 6 weeks in ICU overall. Subsequently risk factors were analyzed separately for tetanus patients and the rest (non-tetanus patients).

There was statistically significant higher risk of VARI in tetanus patients than in non-tetanus patients (Table 5 – 15, Figure 5 – 3). Higher VARI incidence in tetanus patients could be explained by two main things. Firstly, severe tetanus patients take a long time on ventilation, commonly three to four weeks, this is considerable longer than other diseases (Table 5 – 4). This obviously puts tetanus patients at higher risk for VARI than other diseases. Whilst incidence density attempts to correct for the time on ventilation, it seems plausible that risk increases with duration of ventilation as bacteria are able to colonize further into the airway.

Data on second episodes of VAP/ VARI were not collected and it is possible that incidence density may be even higher in tetanus patients as they are more likely to have multiple episodes than those who are ventilated for shorter periods.

Treatment of tetanus involves routine tracheostomy and muscle relaxant use in those who are ventilated therefore it is not surprising that these are also associated with high incidence of VARI. It is possible that it is these treatments increase the risk of VARI in themselves – tracheostomy by providing a shorter access for pathogens to the lower respiratory tract and muscle relaxants/sedatives due to the impaired cough sputum clearance. As tetanus patients who are ventilated all receive these interventions and we did not collect data about the temporal relationship of these interventions to VARI, it is not possible from our data to ascertain whether tetanus itself or its treatment is most linked to VARI. The use of vasopressors in tetanus was significantly related to VARI but their use is indicative of severe disease with longer periods of mechanical ventilation and therefore it is not likely to be a causative factor. Severity level by SOFA and APACHE II scores at ICU admission does not reflect the severity status of tetanus patients because tetanus patients are commonly admitted to ICUs in the early stage of disease, which then progresses to maximum severity in about two weeks before gradually improving [182]. That is why although tetanus patients had statistically lower severity by SOFA and APACHE II score but still had higher VARI incidence than non-tetanus patients (Table 5 – 5).

In non-tetanus patients only thoracentesis was associated with higher risk for VARI (Table 19). The increased VARI risk associated with thoracentesis may relate to the underlying diseases and its severity or physical factors such as difficulty in turning patients and lung atelectasis related to the thoracostomy tube. This result is similar with finding by Oldfield et al that increase in chest tube days was independently associated with higher risk for hospital acquired infection which including VAP [183]. Besides this factor there was no other factors

significantly associated with high VARI incidence (Table 5 – 17, Table 5 – 18, and Table 5 – 19).

In the contrast with the results when the whole patient group was analysed, subgroup analysis by tetanus status (tetanus and non-tetanus) found no significant association between steroid use, tracheostomy or neuromuscular paralysis and VARI incidence. However, stratification by tetanus did not result in any alteration of the direction of (non-significant) association in either group. The association between neuromuscular paralysis and VARI is biologically plausible and in keeping with the literature [181], the loss of significance for this variable in subgroup analysis likely relates to reduction in sample size. For steroid use and tracheostomy there may be other variables confounding the relationship with VARI. The relatively small sample size and heterogeneity of the patients made further analysis to explore this impossible. However when tetanus and non-tetanus patients are viewed, VARI incidence was not statistically significant difference in those with and without steroid therapy and it is likely that this figure is due to the smaller sample sizes of the subgroups and less heterogeneity of non-tetanus subgroup.

5.4.3 Patient characteristics

In the present study the median age of participants was lower than the median age of ICU patients across Vietnam of 61 years, according to the results of a survey at adult ICUs of 14 hospitals across Vietnam, including the three study sites, in 2012 – 2013 [120], and lower than the median age of 61.1 years in European ICUs in 2007 [40] and 60.4 years in Wales in 2012 [184]. This difference may be due to bias in recruiting patients as this study did not routinely recruit all patients admitted to the ICU. However other descriptions of ICU populations from developing countries have shown similar differences in case-mix with younger patients predominating [81].

The proportion of males in this study was 71.4%, which is higher than commonly seen in ICU patients in other studies (ranging from 55.3% to 63.9%) [40, 120, 121, 184]. This male preponderance may reflect the fact that most patients in this study were admitted to ICU due to infectious diseases, sex differences in the manifestation of infectious diseases are recognized, yet poorly understood [185], and a previous study at ICU of NHTD also showed a higher male proportion of 69.5% [118].

Severity of patients in this study was lower as compared to other ICU based studies. Mean and median APACHE II score in this study were 10.9 and 10 points respectively. Whereas mean APACHE II score of ICU patients in the study of Tran Huu Thong et al at Bach Mai Hospital in 2009 – 2013 was 19.4 points. Ary Serpa Neto et al. reported a mean APACHE II score of 18.2 points in a mixed 41 bed ICU in Brazil from 2012 to 2013 [186]. A report by Richard Pugh et al. showed a mean APACHE II score of 16.5 points in 113 patients ventilated for 48 hours or more in ICUs of Wales in 2014 [184]. The low APACHE II score in our study may be explained partly by the low age of our patient population (median age of 52 years) and the relative high proportion of patients who had tetanus, a group with little to no comorbidities: just 9% of tetanus cases had a comorbidity. Furthermore in countries such as Vietnam patients who may normally be admitted to normal wards in high-income settings are often admitted to ICU due to limited monitoring capacity in other departments.

Underlying disease like diabetes put individuals at risk for developing diseases, or more severe disease, and due to multiple medications are challenging to treat with poor outcome as a result. Comorbidities are common in patients admitted to ICUs. The overall proportion of patients with a comorbidity was 38.5% in our study. However, this proportion was significantly different between the three study sites (Table 5 – 1). The proportion of comorbidities in our study was similar to 37.1% in an earlier Vietnamese ICU based study [120]. In that study, the most common comorbidity was stroke sequelae 10.9% (343/3151), followed by diabetes mellitus 9.8% (310/3151), and alcoholism in fifth place with 4.5%

(141/3151). While, alcoholism was the most common comorbidity in our study, accounting for 15% of all participants and diabetes mellitus still in second place with 9.4%. Again the preponderance of infectious disease as a cause of ICU admission may account for this, as alcoholism and diabetes mellitus can increase susceptibility to infections. Johannes Frank et al. found that alcoholism led to extend a hypo-inflammatory of innate immunity mediated through lipopolysaccharide, this condition increased risk for infection [187]. Dao TT et al carried out a survey in reported that people who consumed moderate to heavy alcohol weekly had an increased risk for *Klebsiella pneumoniae* carriage with OR (95% CI) 1.7 (1.04 – 2.8) [188]. Other reasons for the high proportion of alcoholism is that alcohol consumption is common in Vietnam. Kim Bao Giang et al found that 65.5% men and 5.3% women interviewed consumed alcohol in previous week [189]. Van Bui T. et al also found that about 60% Vietnamese men consumed alcohol in a last week and 40% of men were described as 'harmful drinkers' [190]. Although diabetes mellitus prevalence was estimated just around 5.4% of population in 2012, it had doubled from 2.7% in 2002 [191]; it accounted for nearly 10% of patients in our study. Both alcoholism and diabetes mellitus patients in our study had higher VARI incidence although these differences did not reach statistical significance.

Medical interventions that patients had before admission can have important effects on patients' disease progress. If patients were in another hospital before means that patients either progressed or did not recover requiring them to be transferred to the participating ICUs. Though the intention of medical interventions is to improve the health of a patient, they can also put patients at risk. For example, invasive interventions could put patients at risk for hospital acquired infections and antibiotic use could put patients at risk of having disease caused by resistant bacteria. In our study, 75.1% of participants were transferred from another hospital. This means that only 24.9% of ICU patients in this study came directly from community, about half of that in European ICUs, where studies have shown that 50.5% of ICU patients came from community [40]. This difference may be due to our study being carried out at tertiary hospitals whereas European surveillance was carried out on all ICUs in

their network. The high proportion of referred patients also suggests that the three study sites were highly specialized ICUs. Particularly, the high proportion of patients referred from other tertiary hospitals to the ICU of NHTD which accounted for 31.7% of total participants at this site. The proportion of patients intubated at another hospital ranged largely between the study sites (Table 5 – 2). This rate could represent the severity of transferred patients to these study sites and may impact on hospital acquired infection at these study sites. Most patients (86.4%) were given antibiotics on ICU admission, underlining the high burden of infectious diseases in these study sites. This rate was similar to the rate of 84.8% ICU patients used antibiotics in previous point prevalence survey in ICUs across Vietnam suggesting that this burden is shared more widely [120]. However this may also be an important factor in the reduced overall VAP incidence we have found in this study compared to others: as most patients received antibiotics this may have slowed development of subsequent VARI. Antibiotics will be examined in further detail in the following chapter.

In conclusion

This is the largest prospective study on VAP and VARI in Vietnamese ICUs and found that VAP incidence density was 7.6 episodes per 1000 ventilator days according to 2013 CDC criteria for VAP but VARI incidence density was 21.4 episodes per 1000 ventilator days. The large discrepancy between the two suggests that 2013 CDC criteria for VAP did not satisfactorily identify patients treated clinically for respiratory infections in the ICU. Risk factors for VARI are mostly dependent on admission diagnosis, the highest risk factors for VARI were diagnosis of tetanus, septic shock and acute pancreatitis. Particularly, tetanus patients had low SOFA and APACHE II score although they had higher risk for VARI than the other diagnoses. This may be due to inherent differences in the diseases itself or differences in treatment. Studies which include diseases with a protracted requirement for ventilation, such as tetanus should be evaluated more carefully due to the special clinical characteristics and treatments involved.

Chapter 6

Etiology and impact of ventilator-associated pneumonia and ventilator-associated respiratory infection

6.1. Introduction

6.1.1 Impact of ventilator-associated respiratory infections

Ventilator-associated respiratory infections (VARI - a term used to include ventilator associated pneumonia and ventilator associated tracheobronchitis) are the most common infections in intensive care units, with important consequences for patients and healthcare systems.

Although ventilator associated pneumonia (VAP) is associated with increased ICU and hospital stays, hospital cost, and morbidity, the association between VAP and mortality is unclear [46, 48, 51, 67, 170-172]. Although many studies have previously reported higher mortality in patients with VAP, these have usually been retrospective observational studies. More recent studies which have attempted to match control groups and calculate attributable mortality due to VAP. The results from these studies have indicated the relationship may not be so clear. Jordi Rello et al. conducted a retrospective matched cohort study using a large United States inpatient database on patients admitted to an ICU between January 1998 and June 1999 and on mechanical ventilation for > 24 hours. Among 9080 eligible patients, 842 (9.3%) had VAP (defined as a hospital acquired pneumonia diagnosis occurring following intubation for 24 hours or more). These VAP patients were matched with 2243 control patients without VAP. VAP patients had statistically significant longer duration of mechanical ventilation (14.3 vs 4.7 days), ICU stay (11.7 vs 5.6 days), and hospital stay (25.5 vs 14.0 days), (all with $p < 0.001$) [67]. Mean hospital cost per VAP patient was more than 40,000 US$ higher in patients with VAP than without ($p < 0.001$). However, hospital

mortality was not different between VAP patients and control subjects (30.5% vs 30.4% respectively, p = 0.713). Another study using a large United States inpatients database of patients ventilated for at least 2 days and discharged between 1st October 2008 and 31st December 2009 found 88,689 eligible patients, of whom 2383 (2.5%) had VAP with an incidence density of 1.27 per 1000 ventilation days [170]. In a matched cohort, they were able to match 2,144 VAP patients with 2144 without VAP, showing also that VAP patients had longer mean time on ventilation (21.8 vs 10.3 days), ICU stay (20.5 vs 11.6 days), and hospital stay (32.6 vs 19.5 days, all $p < 0.0001$). Mean difference in hospitalization cost of patients with and without VAP was 39,828 US$ ($p < 0.0001$). This study also found that hospital mortality of VAP patients was lower than patients without VAP, 22.5% vs 29.4% respectively, $p < 0.001$. Melsen et al. performed a systematic review of observational studies on VAP and mortality used PubMed, Web of Science, and Embase from its inception through February 2007 and found no evidence of attributable mortality for VAP in trauma and ARDS patients [171]. Observational studies on the sequelae of VAP will inevitably be subject to multiple biases and confounding. As risk of VAP will increased with the number of days on the ventilator, patients that develop VAP will likely have longer ventilation times to the point of diagnosis. This is likely to be associated with factors associated with mortality, even after matching (residual confounding), particularly given the highly heterogenous populations in intensive care. Recognising these limitations, Melsen et al. went on to perform an individual patient meta-analysis of patients enrolled in randomized controlled trials of VAP prevention studies. By analyzing the mortality effect of these preventive measures in 6284 patients from 24 randomized trials they were able to calculate an overall attributable mortality of 13%. However of note they found that this attributable mortality varied markedly across patient types, with no attributable mortality in medical and trauma patients, but very high attributable mortality in surgical patients (69%), further there was no increased risk in those with APACHE II scores < 20 points or in those with very high scores (APACHE II score > 30 points) [68].

The impact of ventilator associated tracheobronchitis (VAT) on outcomes is less clear, due to a lack of precision and consensus in diagnostic criteria and limited research studies. A case control study with participants matched for time on ventilator at VAT onset in addition to five other parameters such as APACHE II score, found that VAT was associated with a doubling of ventilation time and ICU stay, but not with mortality [71]. An early randomized controlled trial of antibiotic therapy for VAT was stopped because of an increased mortality in the control group (no antibiotics) [95]. It is notable that the most common comorbidity in this study was COPD (present in 40% of the intervention arm and 47% of the control arm). A meta-analysis of 17 VAT studies published before 2008 found that VAT was not associated with mortality, nor was treatment of VAT associated with a reduction in mortality, though only 3 trials including that described by Nseir above, addressed the association of treatment with mortality outcome [43]. In a prospective observational study published since the meta-analysis outlined above, 14% of patients who developed VAT went on to develop VAP, the only risk factor for developing VAP was inappropriate antibiotic use [192].

In summary previous research would suggest that VAP has an impact on mortality in some situations, whilst the same appears not to be true of VAT. Both appear to result in prolonged length of ICU stay and ventilation time.

6.1.2 Etiology of ventilator-associated respiratory infections

As discussed earlier, VAP and VAT are believed to have a similar pathogenesis. The overlap in their defining criteria results in a similar microbiological etiology and thus they can be considered together. Most studies have focused on VAP.

The bacterial etiology of VAP and their susceptibility to antibiotics is different between settings. In general, Gram negative bacilli are the predominant pathogens of VAP and the most common pathogens are *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella*

pneumoniae, *Escherichia coli*, and *Staphylococcus aureus* [40, 51, 168, 193, 194]. In developing countries, the predominant bacteria causing VAP tend to be *P. aeruginosa*, *K. pneumoniae*, and *A. baumannii*, with *S. aureus* and other Gram positive bacteria accounting for a smaller proportion [48, 51, 172, 194, 195]. In developed countries, *S. aureus* and *P. aeruginosa* are more common, while *A. baumannii* accounts for a modest proportion [40, 49, 50]. Pathogens of VARI are commonly multidrug resistant bacteria leading to difficulty in treatment. Rosenthal et al. conducted a prospective cohort surveillance on device-associated healthcare-acquired infections in 503 ICUs in 43 countries from 2007 – 2012. The study showed that MRSA accounted for 62.0% of *S. aureus* isolates associated with VAP, and that carbapenem resistance occurred in 77.1% of *A. baumannii*, 42.8% *P. aeruginosa*, 17.2% *K. pneumoniae*, and 7.5% *E. coli* in these cases [45]. Chung et al focused on Asian sites, with prospective data from 73 hospitals in 10 Asian countries (including Thailand, Philippines, but not Vietnam) collected between 2008 and 2009. Bacteria were isolated from 977 cases of VAP, the most common being *Acinetobacter* species, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. Carbapenem resistance was again very high in *Acinetobacter* species (up to 86.7% in cases from Malaysia), with lower rates in *Pseudomonas aeruginosa* (up to 56.9% in China) and *Klebsiella pneumoniae* (up to 4% in China) [196].

In Vietnam, there are limited data in international publications on VAP and its associated bacterial etiology. An 11-year retrospective study at the Hospital for Tropical Diseases in Ho Chi Minh City from 2000 to 2010 described the bacterial pathogens associated with VAP, defined as pneumonia developing after more than two days of ventilation that is ongoing or has been weaned off the day before the pneumonia diagnosis. The study reported that the most common pathogens were *Acinetobacter* spp (30.4%, 206 isolates), *P. aeruginosa* (26.4%, 186 isolates), *K. pneumoniae* (17%, 118 isolates), *Staphylococcus* spp. (8.3%, 53 isolates), and *Streptococcus pneumoniae* (3.1%, 24 isolates) [197]. The investigators found that the proportion of *A. baumannii* resistant to carbapenems increased rapidly from 12.5% in 2007 to 41.7% in 2008 then nearly 90% in 2009 and 2010. Another study from the same

centre from 2011 – 2012 reported that *Acinetobacter* spp. accounted for 94/195 (48.2%) bacteria isolated from suspected VAP through tracheal aspiration, 74 of which were *A. baumannii* with > 80% were resistant to at least three different antibiotics classes, including carbapenems, fluoroquinolones, and cephalosporins [198]. One study on antibiotic susceptibility of 904 *A. baumannii* strains and 529 *P. aeruginosa* strains isolated from hospital-acquired pneumonia or VAP at five hospitals in Vietnam (two in Hanoi and three in Ho Chi Minh City) from 2012 to 2014 found that about 90% of *A. baumannii* were resistant to carbapenems and this resistance pattern had changed a little from 88.6% in 2012 to 95.0% in 2013 then down to 89.4% in 2014. While, the proportion of *P. aeruginosa* resistant to carbapenems rose from about 30% in 2012 to 66.5% in 2014 [199].

The frequency of VAP caused by antibiotic resistant bacteria makes treatment challenging. Although VAP impact on mortality is still controversial, inappropriate or delays in appropriate antibiotic therapy for VAP could result in a considerable increase of mortality and comorbidity [51, 200]. Most VAP management guidelines recommend empirical antibiotics to cover common potential pathogens and selected according to local antibiotic resistance patterns [77, 83, 90, 91].

The aims of this study were to systematically analyse the associated microorganisms, antibiotics treatment and outcome of VAP and VARI in Vietnam. These data would provide evidence for interventions to limit and control VAP as well as ventilator-associated respiratory infections and provide important local data concerning their empiric treatment.

6.2 Methods

A prospective observational study was conducted at three study sites, ICU at National Hospital for Tropical Diseases and Bach Mai Hospital in Hanoi, and ICU at Hospital for Tropical Disease in Ho Chi Minh city. More details of the design and conduct of this study are presented in chapter 2.

6.3. Results

There were 453 patients enrolled in the study from November 2013 to November 2015. Of whom, 79 patients were excluded due to early weaning from mechanical ventilation (69 patients), treatment with ECMO (6 patients), and suspected VAP at enrolment (3 patients), and one patients withdraw from the study. Therefore 374 patients were eligible for analysis, of which 161 (43.1%) were from NHTD, 61 (16.3%) from BMH, and 152 (40.6%) from HTD.

6.3.1. Etiology of ventilator-associated pneumonia and ventilator-associated respiratory infection

There were 37 patients met the definition for VAP, of whom 32 had bacteria isolated from respiratory specimens. A further 55 patients met the definition for other VARI, of whom 41 had possible causative bacteria cultured (table 6-1). In total there were 111 bacterial isolates from 73 patients with VARI (32 VAP and 41 other VARI). 90% of the bacteria were Gram negative. The most frequent isolates were *Acinetobacter baumannii* (32 strains, 28.8%), *Klebsiella pneumoniae* (26 strains, 23.4%), and *Pseudomonas aeruginosa* (24 strains, 21.6%). These three bacteria accounted for approximately three quarters of all bacterial isolates. Among Gram positive bacteria *Staphylococcus aureus* was the commonest isolate (10 strains; 9% of total), followed by *Streptococcus pneumoniae* (3 strains; 2.7% of total). (Table 6 – 1).

Antibiotic resistant bacteria were common. Carbapenem resistance was present in 84.4% (27/32) of *A. baumannii*, 45.8% (11/24) *P. aeruginosa*, and 23.1% (6/26) *K. pneumoniae* (Figure 6 – 1). All of the *Chryseobacterium meningosepticum* and *Escherichia coli* isolates were resistant to carbapenems. All *Haemophilus influenzae*, *Haemophilus haemolyticus*, and *Proteus mirabilis* were susceptible to 3rd generation cephalosporins, and all *Stenotrophomonas maltophilia* were susceptible to sulfamethoxazole and levofloxacin. Among 10 strains of *S.*

aureus, methicillin resistant *Staphylococcus aureus* (MRSA) accounted for 50% (5/10 isolates). *Streptococcus pneumoniae* and *Streptococcus mitis* all were susceptible to penicillin.

Table 6 – 1. Bacterial species cultured from respiratory specimens in those with ventilator-associated respiratory infections (VARI)

Species	VAP, n (%)	Other VARI, n (%)	Total, n (%)
Gram negative bacteria	**40 (83.3%)**	**56 (88.9%)**	**96 (86.5%)**
Acinetobacter baumannii	17 (35.4)	15 (23.8)	32 (28.8)
Klebsiella pneumoniae	9 (18.8)	17 (27.0)	26 (23.4)
Pseudomonas aeruginosa	8 (16.7)	16 (25.4)	24 (21.6)
Haemophilus influenzae	2 (4.2)	3 (4.8)	5 (4.5)
Chryseobacterium meningosepticum	2 (4.2)	1 (1.6)	3 (2.7)
Stenotrophomonas maltophilia	0	3 (4.8)	3 (2.7)
Escherichia coli	1 (2.1)	0	1 (0.9)
Haemophilus haemolyticus	0	1 (1.6)	1 (0.9)
Proteus mirabilis	1 (2.1)	0	1 (0.9)
Gram positive bacteria	**8 (16.7%)**	**6 (9.5%)**	**14 (12.6%)**
Staphylococcus aureus	7 (14.6)	3 (4.8)	10 (9.0)
Streptococcus pneumoniae	0	3 (4.8)	3 (2.7)
Streptococcus mitis	1 (2.1)	0	1 (0.9)
Fungi	**0**	**1 (1.6%)**	**1 (0.9%)**
Candida albicans	0	1 (1.6)	1 (0.9)
Total species	48	63	111

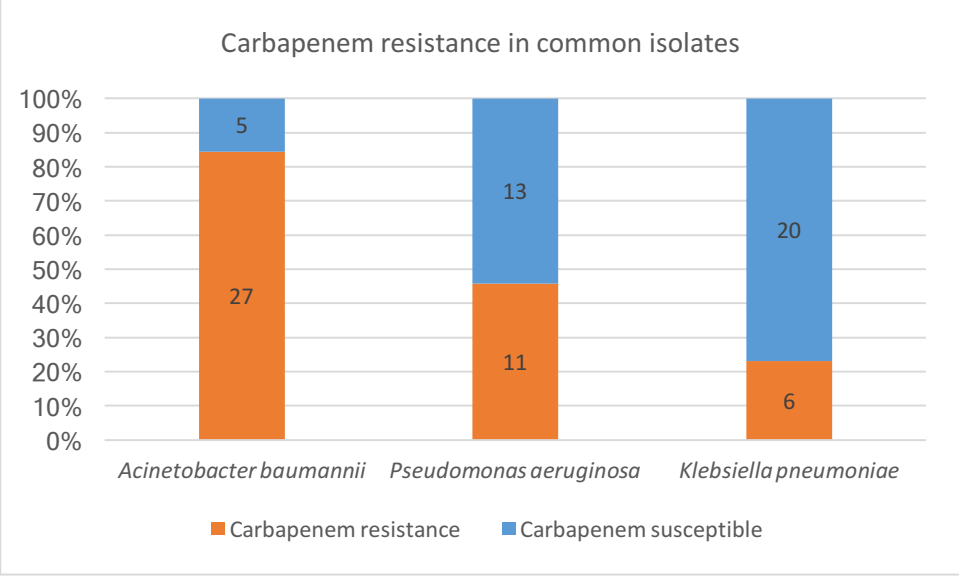


Figure 6 – 1. Carbapenem resistance in common VARI isolates

6.3.2 Impact of VARI

6.3.2.1 General impact of VARI

In total, median (IQR) ventilation time, ICU stay, and cost for ICU stay in all study patients were 12 (6 - 22) days, 20 (12 – 30) days, and 3,005 (1,607 – 5,581) US$. Among 364 patients with known 28-day study outcome status, 62 patients (17.0%) died. There were statistically significant differences between patient with VARI (included VAP) and patients without VARI with respect to ICU stay, ventilation time, and ICU cost. Median (IQR) ventilation time of VARI patients was 21.5 (IQR 15 - 29) compared to 9 (IQR 6 - 19) in those without VARI. Similarly ICU stay was longer in those with VARI: 27.0 days (IQR 21 – 37) compared to 16 days (IQR 10 – 28) ($p < 0.0001$)). Median days of therapy (DOT) of antibiotics use per patient were highest in patients with VAP (35 DOT/patient), then in patients with other VARI (28 DOT/patient), and lowest in patients without VARI (17 DOT/patient). Also there was a difference in antibiotic use by DOT/patient between patients with VARI and patients without VARI, $p < 0.0001$. ICU cost of patients with VARI were significantly higher in patients without VARI: median (IQR) costs were 4723 (2753 – 7795) US$ and 2534 (1291 – 4435) US$ respectively ($p < 0.0001$). However, there were no statistically significant differences in mortality between patients with and without VARI and without VARI. (Table 6 - 2)

In comparing VAP patients with other VARI patients, there were no statistically significant differences in ventilation time, ICU stay, and ICU cost, but mortality was higher in patients with VAP than patients with other VARI: 27.8% and 7.4% respectively with $p = 0.021$. In comparison with patients without VARI, patients with VAP had significant higher in ICU stay, ventilation days, and antibiotics use; although 28-days mortality in patients with VAP (27.8%) was higher than that in patients without VARI (17.5%), the difference was not statistically significant, $p = 0.170$. (Table 6 – 2)

Table 6 - 2. VARI impact on ventilation days, ICU stay, antibiotic use, ICU cost, and mortality

Impact factors	Patients with VARI			Patients without VARI (n=282)	Total patients (n= 374)	P[1] value
	VAP (n=37)	Other VARI (n=55)	Total VARI (n=92)			
ICU stay Median (IQR), (days)	25 (18.5 – 37)	27 (25 – 38)	27 (21 – 37)	16 (10 – 28)	20 (12 – 30)	< 0.0005[a]
Ventilation days, Median (IQR), (days)	21 (13 – 28)	22 (17 – 30)	21.5 (15 – 29)	9 (6 – 16)	12 (6 – 22)	< 0.0005[a]
Antibiotics use, Median (IQR), (DOT/patient)	35 (20 – 54.5)	28 (18 – 39)	29.5 (19 – 45.8)	17 (10 – 26)	20 (12 – 30)	< 0.0005[a]
ICU cost[c], Median (IQR), (US$)	7213 (2828 - 9044)	4196 (2726 - 7193)	4723 (2753 - 7795)	2534 (1291 - 4435)	3005 (1607 - 5581)	< 0.0005[a]
28-day Mortality, n (%)	10/36 (27.8)	4/54 (7.4)	14/90 (15.6)	48/274 (17.5)	62/364 (17.0)	0.748[b]

[1] Between patients with VARI and patients without VARI. [a] Mann Whitney U test, [b] Fisher Exact Test.
[c] 1 US $ = 21246 VND, exchange rate by 30th December 2014.
Comparison between VAP vs other VARI on ICU stay p = 0.220, ventilation days p= 0.423, ICU cost p= 0.140, antibiotics use p = 0.106 (Mann Whitney U test), on mortality p =0.0215 (Fisher Exact Test).
Comparison between VAP vs no VARI on ICU stay, ventilation days, and antibiotics us all p < 0.0005 (Mann Whitney U test), on mortality p = 0.170 Missing mortality (Fisher Exact Test). 10 cases: 2 in VARI and 8 in non-VARI.

6.3.2.2 Impacts of VARI on ICU stay and ventilation days per admission diagnosis

In all patients, median (IQR) ICU stay was longest in those with CNS infection (29 days (16 – 48.5)), followed by those with tetanus (26 days (20 – 35)), pneumonia (14 days (8 – 23)), sepsis and septic shock (13 days (8 – 23)), and the other diagnoses (11 days (7.8 – 15.3)). With the exception of patients with CNS infections, the median ICU stays of patients with VARI were significantly longer than in patients without VARI. (Table 6 – 3).

Median ventilation time of patients with VARI were about two to three times longer than these of patients without VARI in all five admission diagnosis categories (Table 6 – 4).

Table 6 - 3. VARI and length of ICU stay (in days) by admission diagnosis

Diagnosis	All patients		Patients without VARI		Patients with VARI		P[a] value
	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)	
Pneumonia	73	14 (8 – 23)	66	14 (8 – 21)	7	23 (18 – 33)	0.021
Sepsis & shock	55	13 (8 – 23)	44	11.5 (7 – 15)	11	26 (16 – 49)	0.001
Tetanus	132	26 (20 – 35)	84	23 (17 – 30)	48	29.5 (25 – 37.8)	< 0.0005
CNS infection	60	29 (16 – 48.5)	49	30 (15.5 – 47)	11	26 (21 – 60)	0.417
The others	54	11 (7.8 – 15.3)	39	10 (7 – 13)	15	19 (14 – 26)	< 0.0005

[a] Mann Whitney U test comparing patients with and without VARI

Table 6 - 4. VARI and days on mechanical ventilation by admission diagnosis

Diagnosis	Total patients		Patients without VARI		Patients with VARI		P[a] value
	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)	
Pneumonia	73	9 (6 – 15.5)	66	8 (5.8 – 14)	7	20 (14 – 28)	0.006
Sepsis & shock	55	8 (6 – 13)	44	6.5 (5 – 9.8)	11	22 (15 – 34)	< 0.0005
Tetanus	132	17.5 (13 – 24)	84	15 (10 – 21.3)	48	23 (18.3 – 29)	< 0.0005
CNS infection	60	14 (7.3 – 33)	49	11 (6.5 – 29)	11	26 (14 – 42)	0.043
Others	54	6 (4 – 9.3)	39	5 (4 – 7)	15	12 (7 – 25)	< 0.0005

[a] Mann Whitney U test comparing patients with and without VARI

6.3.2.3 Impact of VARI on systemic antibiotics use

Total systemic antibiotics consumption

In total, there were 657 antibiotics courses for community acquired infections, 353 courses for hospital acquired infections, 97 courses for ventilator associated pneumonia, and 24 courses for prophylaxis. Median duration courses were 7.0 days (IQR 3.5 – 9.5) for community infection, 7.0 days (IQR 4.0 – 12.0) for hospital acquired infection, 8.0 days (IQR 5.0 – 11.0) for VAP, 4.0 days (IQR 3.0 – 8.0) for prophylaxis. Overall, antibiotic consumption in ICU in the study follow up period was 117.2 DOT/100 patient days, of which 49.2 DOT (42.0%, 49.2/117.2) was for hospital acquired infections (9.4% for VAP and 32.6% for other HAI) and 66.1 DOT (56.4%, 66.1/117.2) for community acquired infections. The five most common antibiotics used were carbapenems (32.3%), fluoroquinolones (16.0%), imidazole derivatives (10.5%), colistin (9.6%), and combinations of penicillins included beta-lactamase

inhibitors (7.0%). These antibiotics accounted for 75.4% of total DOT/100 patient days. Most polymyxins and over two thirds of penicillin/beta-lactamase inhibitor combinations were used for HAI, whilst the indication for carbapenem use was more evenly spread across community and hospital acquired infection. Interestingly, 8.8% of colistin was used for community acquired infections including 6 cases: 1 septic shock, 2 pneumonia, 2 COPD, 1 pancreatitis at ICU of BMH. More details were presented in Table 6 – 5.

Table 6 - 5. Antibiotic consumption by indication (DOT/100 PD)

Type of antibiotics	CAI	HAI	Prophylaxis	Total, (%)
Carbapenems, (%)	19.9 (52.5)	17.7 (46.7)	0.3 (0.8)	37.9 (32.3)
Fluoroquinolones, (%)	14.2 (75.9)	4.2 (22.5)	0.4 (2.1)	18.7 (16.0)
Imidazole derivatives, (%)	12.0 (96.7)	0.1 (0.8)	0.2 (1.6)	12.3 (10.5)
Polymyxins (Colistin), (%)	1.0 (8.8)	10.3 (91.2)	0.0	11.3 (9.6)
Combinations of penicillins included beta-lactamase inhibitors, (%)	2.4 (29.3)	5.5 (67.1)	0.4 (4.9)	8.2 (7.0)
Third-generation cephalosporins, (%)	4.7 (63.5)	2.4 (32.4)	0.3 (4.1)	7.4 (6.3)
Glycopeptide antibacterials, (%)	3.0 (43.5)	3.7 (53.6)	0.3 (4.3)	6.9 (5.9)
Other antibacterials[a], (%)	1.9 (47.5)	2.1 (52.5)	0.0	4.0 (3.4)
Other aminoglycosides, (%)	1.0 (37.0)	1.7 (63.0)	0.0	2.7 (2.3)
Beta-lactamase sensitive penicillins, (%)	2.3 (100)	0.0	0.0	2.3 (2.0)
Penicillins with extended spectrum, (%)	1.1 (84.6)	0.2 (15.4)	0.0	1.3 (1.1)
Beta-lactamase resistant penicillins, (%)	0.6 (54.5)	0.5 (45.5)	0.0	1.1 (0.9)
Macrolides, (%)	0.6 (85.7)	0.1 (14.3)	0.0	0.7 (0.6)
Tetracyclines, (%)	0.5 (83.3)	0.1 (16.7)	0.0	0.6 (0.5)
Combinations of sulfonamides and trimethoprim, incl. derivatives, (%)	0.3 (50)	0.3 (50)	0.0	0.6 (0.5)
Lincosamides, (%)	0.5 (100)	0.0	0.0	0.5 (0.4)
Fourth-generation cephalosporins, (%)	0.2 (66.7)	0.1 (33.3)	0.0	0.3 (0.3)
Nitrofuran derivatives, (%)	0.0	0.3 (100)	0.0	0.3 (0.3)
Amphenicols, (%)	0.1 (50)	0.1 (50)	0.0	0.2 (0.2)
Total AB use, (%)	66.1 (56.4)	49.2 (42.0)	1.9 (1.6)	117.2 (100)

CAI: community acquired infections, HAI: hospital acquired infections.
[a] Other antibacterials: fosfomycin and linezolid.

Impact of VARI and admission diagnosis on antibiotics consumption

Median (IQR) DOT per patient with VARI was two to three times higher than that per patient without VARI in each group of admission diagnosis and these differences were statistically significant exception for CNS infection (p = 0.289). Highest antibiotics consumption was in pneumonia and septic & shock patients with VARI where median (IQR) DOT were 61 (30 – 86) days and 58 (42 – 93) days, respectively. Overall, median (IQR) DOT/patients with VARI

was 29.5 (19.0 – 45.8) days while in patients without VARI it was 17 (10 – 26) days ($p < 0.0005$). (Table 6 – 6a).

Table 6 - 6a. Antibiotic use in DOT/patient by VARI status and admission diagnosis

Diagnosis	Total patients		Patients without VARI		Patients with VARI		P[a] value
	No. of pts	Antibiotics use in DOT/patient, Median (IQR)	No. of pts	Antibiotics use in DOT/patient, Median (IQR)	No. of pts	Antibiotics use in DOT/patient, Median (IQR)	
Pneumonia	73	25 (17 - 38.5)	66	23.5 (16 - 32.8)	7	61 (30 - 86)	0.005
Sepsis & shock	55	26 (15 - 43)	44	22 (13.3 - 28.8)	11	58 (42 - 93)	< 0.0005
Tetanus	132	18 (10 - 28.7)	84	13.5 (8.3 - 20)	48	27 (18.3 - 35)	< 0.0005
CNS infection	60	16 (7 - 28)	49	15 (7 - 28)	11	18 (15 - 31)	0.289
The others	54	19 (12.8 - 28.3)	39	17 (10 - 22)	15	32 (20 - 44)	< 0.0005
Total	374	20 (12 – 30)	282	17 (10 - 26)	92	29.5 (19 - 45.8)	< 0.0005

[a] Mann Whitney U Test comparing patients with and without VARI

I calculated day of therapy/patient day in ICU in the study follow up by dividing total DOT for number of ICU days for each patient. Overall, median (IQR) DOT/PD was 1.13 (0.80 – 1.97) in patients with VARI and 1.05 (0.61 – 1.86) in patients without VARI ($p = 0.171$). Median (IQR) DOT/PD in patient with and without VARI in subgroup of admission diagnosis respectively was 2.68 (2.00 – 3.00) vs 1.77 (1.21 – 2.21) in pneumonia, 2.46 (2.00 – 2.72) vs 1.83 (1.07 – 2.15) in sepsis & septic shock, and 0.99 (0.72 – 1.21) vs 0.60 (0.41 – 0.90) in tetanus ($p < 0.05$ for all). (Table 6 – 6b).

Table 6 – 6b. Antibiotic use in DOT/PD by VARI status and admission diagnosis

Diagnosis	Total patients		Patients without VARI		Patients with VARI		P[a] value
	N	Antibiotics use in DOT/PD, median (IQR)	N	Antibiotics use in DOT/PD, median (IQR)	N	Antibiotics use in DOT/PD, median (IQR)	
Pneumonia	73	1.88 (1.25 – 2.44)	66	1.77 (1.21 – 2.21)	7	2.68 (2.00 – 3.00)	0.038
Sepsis & shock	55	1.96 (1.42 – 2.33)	44	1.83 (1.07 – 2.15)	11	2.46 (2.00 – 2.72)	0.003
Tetanus	132	0.72 (0.49 – 1.00)	84	0.60 (0.41 – 0.90)	48	0.99 (0.72 – 1.21)	< 0.0005
CNS infection	60	0.82 (0.39 – 1.18)	49	0.82 (0.38 – 1.25)	11	0.82 (0.56 – 1.14)	0.535
The others	54	1.68 (1.18 – 2.00)	39	1.67 (1.20 – 2.00)	15	1.75 (1.07 – 2.00)	0.900
Total	374	1.10 (0.66 – 1.87)	282	1.05 (0.61 – 1.86)	92	1.13 (0.80 – 1.97)	0.171

[a] Mann Whitney U Test

Systemic antibiotics use at the study sites by VARI status and indications

The total antibiotic use was 117.2 DOT/100 PD in ICUs. Antibiotic use was highest at Bach Mai Hospital ICU (BMH) with 210.1 DOT/100 PD, then at National Hospital for Tropical Diseases ICU (NHTD) with 139.6 DOT/100 PD, and lowest at Ho Chi Minh Hospital for Tropical Diseases ICU (HTD) with 72.6 DOT/100 PD. There was a small difference in the antibiotic consumption between patients with and without VARI. Figure 6 – 2.

Looking at the antibiotics prescribed for hospital acquired infection (HAI), there was a large difference between patients with and without VARI, 82 vs 34.1 DOT/100 PD, corresponding to 62.3% and 30.9% of total antibiotics consumption in DOT/100 PD respectively. These proportions were similar at all 3 study sites. The Proportion of antibiotic use for HAI in patients with VARI was much higher than that in patients without VARI, 60.8% (92.5/152.2) vs 28.5% (38/133.7) at NHTD, 66.3% (145.8/219.9) vs 30.3% (62.1/205.1) at BMH, and 61.9% (54.4/87.9) vs 36.0% (23.7/65.7) at HTD. Figure 6 – 2.

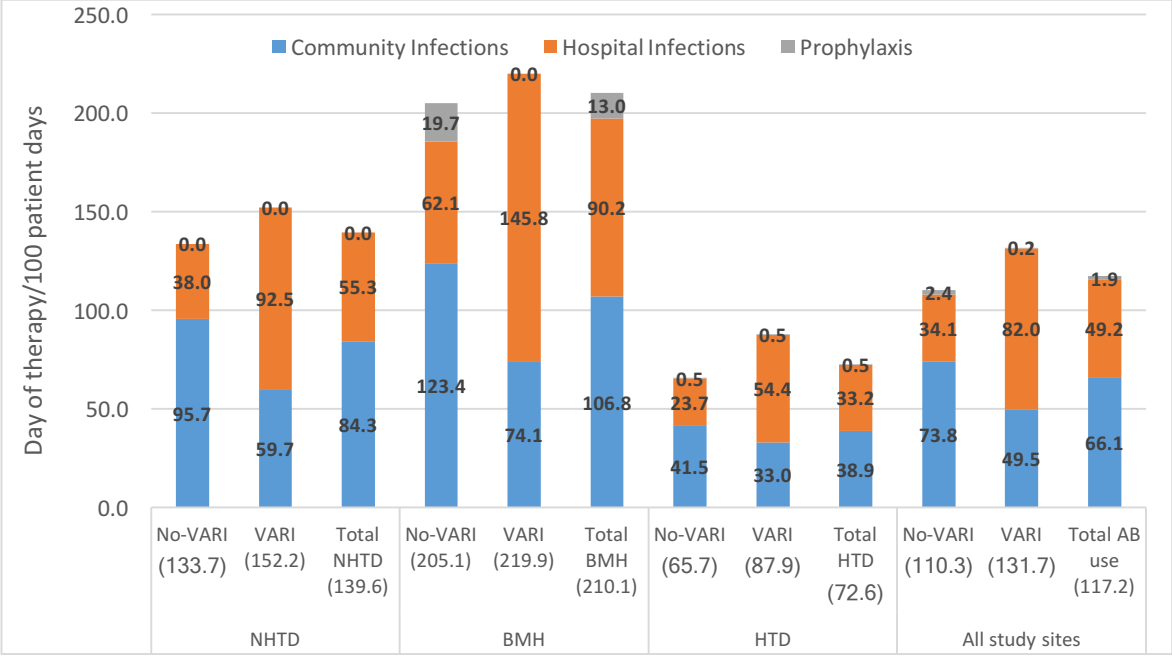


Figure 6 – 2. Indications for systemic antibiotic use by VARI status at three sites

The greatest use of carbapenems and colistin was at BMH with 75.7 and 41.3 DOT/100 PD respectively, accounting for 55.7% (117/210.1) of total DOT/100 PD. These two types were used higher in patient with VARI than in patients without VARI. Only at BMH was colistin used for community acquired infection. More details were presented in Figure 6 – 3.

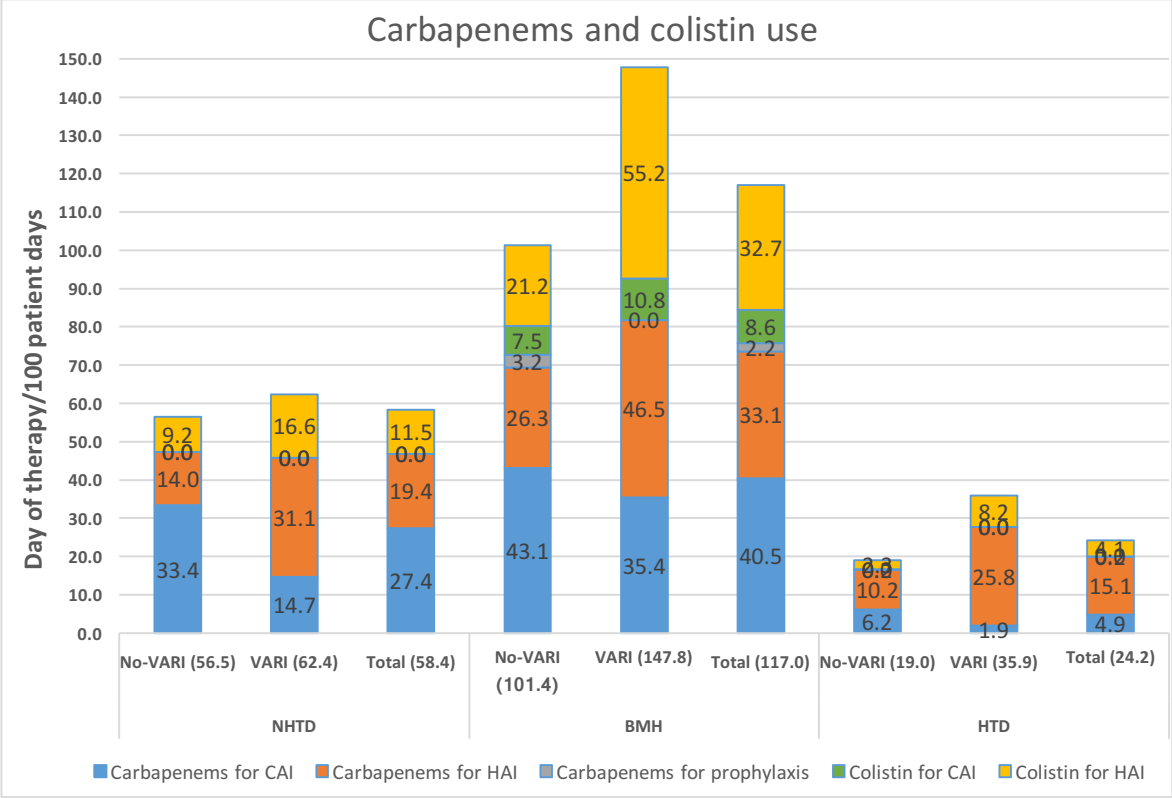


Figure 6 – 3. Carbapenem and colistin consumption and indication at the study sites

Table 6 - 7. ICU costs for patients with and without VARI by admission diagnosis

Diagnosis	Total patients		Patients without VARI		Patients with VARI		P[a] value
	N	Median (IQR), (US$)	N	Median (IQR), (US$)	N	Median (IQR), (US$)	
Pneumonia	73	3250 (1887 – 7004)	66	2941 (1841 – 6239)	7	7807 (3434 – 11974)	0.045
Sepsis & shock	55	3473 (2136 – 6887)	44	3064 (1906 – 5203)	11	7931 (4797 – 13436)	< 0.0005
Tetanus	132	2170 (1474 – 4052)	84	1616 (1206 – 2776)	48	3871 (2196 – 6431)	< 0.0005
CNS infection	60	3389 (1548 – 6261)	49	2929 (1425 – 6235)	11	4144 (2832 – 6974)	0.298
The others	54	3298 (1795 – 6207)	39	2994 (1579 – 4577)	15	7193 (2629 – 7810)	0.002

[a] Mann Whitney U test

6.3.2.4 VARI impact on ICU cost

The highest median cost for ICU stay was incurred by sepsis and septic shock patients (3473 US$), followed by CNS infections (3389 US$), the other diagnoses (3298 US$), pneumonia (3250 US$), and lowest in tetanus patients (2170 US$). Except for those admitted with CNS infections, the median ICU cost of patients with VARI was approximately double that of patients without VARI. (Table 6 – 7).

6.3.2.5 VARI impact on 28-day mortality

During the 28 day study period, there were 10 (2.7%) patients who were lost to follow up (all 10 in the non-tetanus group). 364 patients completed follow-up of which 302 (83.0%) patients were alive, and 62 (17.0%) patients died (45 patients died in the study hospital, 12 after transfer to another hospital, and 5 at home). At discharge, 71 (19.0%) patients died, 6 (1.6%) were classified as missing (due to transferring to other departments), and 297 (79.4%) patients were alive.

In total, the 28 day mortality in patients with VAP was 27.8% (10/27), in patients with other VARI (not VAP) was 7.4% (4/54), and in patients without VARI was 17.5% (48/274). In the non-tetanus group mortality was 26.3% (61/232); in those with VAP mortality was 45.5% (10/22), whereas in patients without VARI it was 25.3% (48/190), and in patients with other VARI mortality was 15.0% (3/20). Among non-tetanus patients, patients developing VAP had a higher odds ratio for death compared with patients who never developed VARI, odds ratio 2.47 (95% CI 1.00 – 6.07, p = 0.05). Interestingly mortality in patients with other VARI was lower than that in patients never developed VARI [odds ratios 0.38 (0.13 – 1.09) in total patients and 0.52 (0.15 - 1.86) for non-tetanus patients], although these differences were not statistically significant. In tetanus patients, there was only one death making mortality was just 0.8% (Table 6 – 8). Among 22 non-tetanus patients with VAP, mortality was 50% (8/16) in patients with carbapenem resistant isolates, 40% (2/5) in patients without any isolate, and

none in one patient isolated MSSA. There was no mortality among 14 tetanus patients with VAP (including 5 patients with carbapenem resistant isolates).

Table 6 - 8. Impact of VAP and VARI on 28-day mortality

VARI status	Total patients				Non-tetanus patients				Tetanus patients	
	Alive	Death	Odds ratio (95% CI)	P[a] value	Alive	Death	Odds ratio (95% CI)	P[a] value	Alive	Death
VAP, n (%)	26 (72.2)	10 (27.8)	1.81 (0.82 - 4.00)	0.142	12 (54.5)	10 (45.5)	2.47 (1.00 – 6.07)	0.050	14 (100)	0
Other VARI, n (%)	50 (92.6)	4 (7.4)	0.38 (0.13 – 1.09)	0.072	17 (85.0)	3 (15.0)	0.52 (0.15 – 1.86)	0.316	33 (97.1)	1 (2.9)
Non-VARI, n (%)	226 (82.5)	48 (17.5)	Reference		142 (74.7)	48 (25.3)	Reference		84 (100)	0
Total, n (%)	302 (83.0)	62 (17.0)			171 (73.7)	61 (26.3)			131 (99.2)	1 (0.8)

Mortality in VAP higher than in other VARI with odds ratios (95% CI) 4.81 (1.37 – 16.83), p = 0.014; in non-tetanus odds ratios (95% CI) 4.72 (1.07 – 20.89), p = 0.041 (univariate logistic regression).
[a] Univariate logistic regression

VARI impacts on mortality by admission diagnosis

In total, 28-day mortality was highest in patients with sepsis and septic shock (34.5%), followed by those with pneumonia (29.6%), other diagnoses (28.3%), CNS infections (13.3%), and tetanus (0.8%). In pneumonia and sepsis/septic shock patients, mortality in patients with VARI was higher than patients without VARI (57.1% vs 26.6% and 45.5% vs 31.8% respectively). In CNS infections and the other diagnoses, mortality in patients with VARI was lower than patients without VARI, 9.1% vs 14.3% and 23.1% vs 30.3% respectively. However, none of these differences were statistically significant. (Table 6 – 9).

Table 6 - 9. VARI and 28 study day mortality by admission diagnosis

Admission diagnosis	Mortality in VARI patients, %			Mortality in patients without VARI, %	Mortality in total patients, %	P[1a] value	P[2a] value
	VAP	Other VARI	All VARI				
Pneumonia	57.1 (4/7)	0 (0/0)	57.1 (4/7)	26.6 (17/64)	29.6 (21/71)	0.184	0.184
Sepsis & shock	50.0 (3/6)	40.0 (2/5)	45.5 (5/11)	31.8 (14/44)	34.5 (19/55)	0.485	0.396
Tetanus	0 (0/14)	2.9 (1/34)	2.1 (1/48)	0 (0/84)	0.8 (1/132)	0.364	
CNS infection	0 (0/1)	10.0 (1/10)	9.1 (1/11)	14.3 (7/49)	13.3 (8/60)	1.00	1.0
The others	37.5 (3/8)	0 (0/5)	23.1 (3/13)	30.3 (10/33)	28.3 (13/46)	0.729	0.692

[a] Fisher's Exact test, [1] between VARI & without VARI, [2] between VAP & without VARI. Missing 10 cases: 2 cases in pneumonia patients and 8 cases in others admission diagnosis.

VARI impacts on mortality by VARI empiric treatment

Mortality in patients with VAP or VARI receiving adequate empiric treatments (pathogens isolated from respiratory specimen at the beginning of empiric treatment was susceptible to at least one of antibiotic agents used) was higher than patients received inadequate empiric treatment, odds ratios (95% CI) 1.09 (0.17 – 7.06) and 1.98 (0.39 – 10.08) respectively. However, these differences were not statistically significant. (Table 6 – 10).

Table 6 - 10. Empiric VAP and VARI treatment and 28 study day mortality

Patients with	Empiric treatment	Alive	Death	OR (95% CI)	P[a] value
VAP	Adequate, n (%)	16 (76.2)	5 (23.8)	1.09 (0.17 – 7.06)	0.925
	Inadequate, n (%)	7 (77.8)	2 (22.2)	Reference	
VARI (included VAP)	Adequate, n (%)	41 (82.0)	9 (18.0)	1.98 (0.39 – 10.08)	0.413
	Inadequate, n (%)	18 (90.0)	2 (10.0)	Reference	

[a] Univariate logistic regression.
Among 54 patients with other VARI, 29 cases had adequate treatment (4 died), 11 cases had inadequate treatment (0 died), and 14 unknown adequacy of treatment (0 died).

VARI impact on 28-day mortality adjusted for age gender and APACHE II score

In multivariate analysis, VARI had no statistically significant impact on mortality, although VAP had higher risk for death compared to patients without VARI (odds ratio 1.93 (95% CI 0.73 – 5.11)). APACHE II score had statistically significant higher risk for death with odds ratios 1.07 (95% CI 1.01 – 1.15; p=0.034) for each one-point score increase. In comparison with CNS infection, only tetanus patients had lower risk for death with odds ratios 0.06 (95% CI 0.01 – 0.59); p = 0.015). Other admission diagnosis categories had higher risk for death but did not reach statistical significance. (Table 6 – 11).

Table 6 – 11. Impact of VARI on mortality adjusted for severity and admission diagnosis

Risk factors		Odds ratio (95% CI)	P[a] value
Age (year)		1.02 (0.998 – 1.04)	0.074
Male gender		0.97 (0.49 – 1.91)	0.918
VARI status	VAP	1.93 (0.73 – 5.11)	0.184
	Other VARI	0.62 (0.16 – 2.37)	0.482
	Non VARI	Reference	
Diagnosis	Sepsis & septic shock	2.46 (0.87 – 6.92)	0.089
	Pneumonia	1.75 (0.62 – 4.91)	0.291
	Other illnesses	1.99 (0.68 – 5.82)	0.210
	CNS infections	Reference	
	Tetanus	0.06 (0.01 – 0.59)	0.015
Severity	APACHE II (points)	1.07 (1.01 – 1.15)	0.034

[a] Multivariate logistic regression

6.4 Discussion

In this multicenter observational study for about two year (2013 – 2015), there were total 374 patients in final analysis, of which 37 patients developed VAP and 55 patients developed other VARI. Gram negative bacteria accounted for nearly 90% of total pathogens isolated from VARI patients, with predominance of *A. baumannii, K. pneumoniae*, and *P. aeruginosa* and their high proportion of carbapenems resistance. Patients with VARI had significant higher in amount of ICU stay, ventilation days, antibiotics use, and ICU cost than those in patients without VARI.

6.4.1 Etiology

Our study found that Gram negative bacteria were the predominant pathogens associated with VARI (86.5%) and the most common species were *A. baumannii, K. pneumoniae*, *P. aeruginosa,* and *S. aureus* (Table 6 – 1). Carbapenem resistance was highest in *A. baumannii* (84.4%), then *P. aeruginosa* (45.8%), and *K. pneumoniae* (23.1%) (Figure 6 – 1), and all *C. meningosepticum* and *E. coli* isolated. MRSA accounted for 50% *S. aureus* (5/10 isolates). These findings are in line with other studies. Ling et al. in a systematic review on hospital

acquired infection in Southeast Asia found that common pathogens of VAP were *Acinetobacter* spp., *Pseudomonas* spp., and *Klebsiella* spp. (data from 2 studies in Malaysia, one in Singapore, and two in Thailand, published from 2001 to 2011) [172]. Arabi et al. in a systematic review on VAP in adult in developing countries (papers published from 1966 to 2007) found that Gram negative bacilli were the most important VAP pathogens, ranging from 41% to 92%, and most common isolates were *P. aeruginosa* and *Acinetobacter* spp [48]. Inchai et al. conducted a retrospective study on 621 patients with VAP according to 2005 ATS/IDSA criteria in medical ICU of Chiang Mai university hospital from January 2005 to December 2011 [51]. They found that four most common pathogens of VAP were *A. baumannii* (54.3%, 337/621), with 65.3% carbapenem resistant and 3.6% resistant to all antibiotics; *P. aeruginosa* (35.2% (191/621)); MRSA (15.1% (94/621)); and *K. pneumoniae* (10.8% (67/621)). A study in adult ICU of King Abdulaziz Medical City in Saudi Arabia from 2004 - 2009 also found that most common pathogens for VAP were *Acinetobacter* spp. and *P. aeruginosa* with high proportion of carbapenems resistance, 70.8% and 30.6% respectively [194]. These evidences support that most common pathogen of VAP was Gram negative bacilli with predominance of *A. baumannii*, *P. aeruginosa*, *K. pneumoniae*, and *S. aureus* and high rate of carbapenem resistance and MRSA. These pathogens should be addressed in infection control program for prevention and limitation VAP incidence.

6.4.2 Impact of VARI

In our study, patients with VARI had statistically about double times higher in ICU stay, ventilation time, antibiotics use, and ICU cost these factors compared with patients without VARI (Table 6 – 2). Other studies on VAP also found that patient with VAP had two to three times higher in ventilation time, ICU stay, and hospital cost compared with patients without VAP [67, 170]. However, there was not statistically different in these parameters between VAP patients and other VARI patients in our study. And I did not find any comparison between VAP and other VARI like this. Nseir et al. conducted a retrospective case control

study on ventilated patients with immunocompetent, non-trauma, and without chronic respiratory failure found that patients with VAT (one type of VARI) had median duration in ICU stay and ventilation days about double of those in patients without VAT, 24 vs 12 days and 17 vs 8 days, respectively [71]. Impacts of other VARI could perhaps be explained by an increased sputum secretion due to VARI as excessive sputum secretion is one cause of difficulty when weaning from mechanical ventilation [201]. With more sputum, these patients were difficult to wean from ventilator because they rapidly became fatigue on spontaneous breathing and that lead to need longer ventilation support until VARI was treated to until having normal or less sputum secretion that patients could compensate for it. This means that burden of other VARI is also important as VAP on these aspects and should be set as a target of infection control practice.

6.4.2.1 Impact on ventilation time and ICU stay

Due to the wide difference between admission diagnoses on ICU stay, subgroup analysis was performed based on admission diagnoses for more homogeneity.

Exception for CNS infections, ICU stay and ventilation time of patients with VARI were higher than patients without VARI in all admission diagnosis categories. This finding is consistent with the majority of published literature [67, 170, 202-204]. Overall, absolute ventilation time and ICU stay between patients with VARI (VAP) and without VARI in our study were longer than those in other studies which may be due to differences in case-mix or differences in weaning practice or different criteria for discharge from ICU. Kollef et al. reported that mean ventilation time and ICU stay between patients with and without VAP were 21.8 vs 10.3 day and 20.5 vs 11.6 days, respectively, $p < 0.0001$ [170]. Rello et al. reported these in patients with VAP and without were 14.3 vs 4.7 days and 11.7 vs 5.6 days [67]. Erbay et al. conducted a retrospective case control study in Turkey from January 1st 2000 to December 31st 2002 found that median ICU stay in patients with VAP and without were 8.0 vs 2.5 days with $p < 0.0001$ [204]. Mathai et al. by prospective observational study

on 250 adult patients ventilated for > 48 hours in North of India found that median ICU stay in patients with and without VAP were 13 vs 6 days, $p < 0.001$ [46].

6.4.2.2 Systemic antibiotics use and VARI

Total systemic antibiotics use

In total, systemic antibiotic use was 117.2 DOT/100 patient days and 94.1% was used for infection treatment with 42.0% for hospital acquired infections and 52.1% for community acquired infections: the remaining 5.9% antibiotics use was for prophylaxis (Table 6 – 5). Antibiotic consumption in European ICUs in 2007 were 131.8 DOT/100 ICU days with 76.3% was for anti-infection use, 22% for prophylaxis, and 1.7% for selective digestive decontamination [40]. Antibiotics consumption by DOT/100 PD in our study was less than in European ICUs despite the majority of patients being admitted with infectious diseases is surprising. However our case-mix includes patients with relatively long ICU stays, and thus may have led to decreased antibiotic consumption measured by DOT/100 PD as they remained in ICU after the original antibiotic course was finished. Mean ICU stay in our study was 24.2 days (Table 6 – 2), while that in European ICUs was just 10.2 days.

The proportion of carbapenems (32.3%) and polymyxin (9.6%) in total DOT of antibiotics use in our study was much higher than these in European ICUs, 18.6% and 2.0% respectively [40]. This could be due to high level of antibiotic resistance or the different antibiotic prescription habits of physicians in our study sites. Most common pathogen of VARI were *A. baumannii*, *P. aeruginosa*, and *K. pneumoniae* with high level of carbapenems resistance, 84.4%, 45.8%, and 23.1%, respectively (Table 6 – 1 & Figure 6 – 1).

VARI status and total systemic antibiotics use

Antibiotic use by median DOT/patient and DOT/PD in patients with VARI were statistically higher than those in patients without VARI for all patients and subgroups with specific diagnosis categories of pneumonia, sepsis and septic shock, and tetanus except for CNS

infections and other diagnostic categories (Table 6 – 6a and Table 6 - 6b). This exception could be due to heterogeneity of patients with CNS infection and other diagnosis. For example, acute bacterial CNS infections commonly require ventilation for a short time and usually receive antibiotics for two to three weeks, while viral encephalitis patients are usually not given antibiotics but require ventilation and ICU for longer periods, so these patients have a higher risk for hospital acquired infections including VARI, although are using less antibiotics. Therefore, antibiotics use should be evaluated among patients with more homogeneity.

VARI status and systemic antibiotics use at the study sites

Antibiotics use by DOT/100 PD were wide different between the study sites. Antibiotics use at BMH (210.1) was about 1.5 times higher than that at NHTD (139.6) and triple higher than that at HTD (72.6 DOT/100 PD). The high antibiotics use at BMH could be explained a part by differences in case-mix and duration of patient stay. In patients with VARI 62.3% of antibiotics used were for HAI (similar in all study sites) while in patients without VARI this proportion was 30.9% (ranged 28.5% to 36.0% between study sites). This means that besides VARI, other HAIs remain common causes for antibiotic prescription within the ICU. (Figure 6 – 2).

6.4.2.3 VARI impact on hospital costs

Our study found that ICU cost of patients with VARI was statistically higher than that of patients without VARI, median ICU cost of VARI patients was about double of patients without VARI, 4723 vs 2534 US$ respectively (Table 6 – 2). In each admission diagnosis category, VARI patients had ICU cost statistically higher than patients without VARI, exception for patients with CNS infections (Table 6 – 7). Although CNS infection patient with VARI had higher ICU cost than CNS infection patients without VARI, the difference did not reach statistically significant. This may be that CNS infections was more heterogeneity of

illnesses with short and long time need to treat, or relatively small number of CNS infections patients with VARI,

Rello et al. found that in the United State mean hospital cost for patients with VAP was statistically higher than patients without VAP, 104983 vs 63689 US$ respectively, in 1998 - 1999 [67]. Kollef et al found that in the United State hospital cost for patients with VAP was 99598 US$ and patients without VAP was 59770 US$ in 2009 with $p < 0.0001$ [170]. Machai et al. conducted a prospective study on patients ventilated > 48 hours at adult tertiary ICU in North of India in 2010 – 2011 found that median hospital cost for patients with VAP and without was 6350.9 and 2598.8 US$ respectively, $p < 0.0001$ [70]. Erbay et al. conducted a retrospective study in a anaesthesiology ICU in Pamukkale university hospital, Turkey, in 2000 to 2002 reported that hospital cost for patient with and without VAP were 2839.3 and 653.4 US$ respectively, $p < 0.0001$ [204]. This evidences shows that cost for patients with VAP/VARI is often two times to four times higher than cost for ICU patients without VAP/VARI. Given the incidence of VARI of 25% reported in my study (chapter 5), VARI represents a significant economic burden in Vietnam. Prevention of VARI would result in significant cost savings.

6.4.2.4 VARI impacts on mortality in 28 study days

The 28-day mortality of patients with VAP (27.8%) was higher than patients without any VARI (17.5%), but did not reach statistical significance (Table 6 – 8). The mortality rate was lower than that reported in some other studies from the United States, Europe, to neighboring countries of Vietnam [47, 51, 67, 205]. Many previous studies have used different criteria to define VAP than our study and this may be a cause for the difference.

Furthermore low mortality in current study could be explained by a large number of tetanus patients. A high proportion of tetanus patients (36.4%, 48/132 patients) developed VARI (Chapter 5) but its mortality was very low: no patients died among 14 patients with VAP, and

only one patient (2.9%) died in 34 patients with other VARI (not VAP). After tetanus patients were excluded from the analysis for mortality, 28-day mortality in VAP patients was much higher at 45.5% (Table 6 – 8). This rate was similar with mortalities of VAP patients reported from Thailand (44.4%) [51], China (41.9% and 43.2%) [47], and Europe (35% - 51%) [205]. However, mortality of non-tetanus patients with VAP was much higher than mortality of 30.5% in the United State reported by Rello et al. [67].

Mortality in patients with other VARI (not VAP) was significantly lower than that in patients with VAP both in total patients and in non-tetanus patients (Table 6 – 8). This could be because other VARI patients were treated with less severe and earlier infection than VAP patients. Earlier treatment of VARI may have prevented subsequent VAP and thereby reduced mortality. Jordi Rello and colleagues proposed that VAP could develop from VAT (or other VARI) [37]. Martin-Loeches et al. performed a multicentre, prospective, observational study at 114 ICUs on 2690 eligible patients (age > 18 years, ventilated for > 48 hours) from September 1st 2013 to July 31st 2014 [32]. There were 689 (23%) patients developed VARI, of which 320 (11%) VAT and 369 (12%) VAP. The authors found that secondary VAP from VAT patient was 8% (19/250) in VAT patients received appropriate VAT treatment and 29% (20/70) in VAT patients with inappropriate VAT treatment. In addition, Dallas et al. found that there was no statistically significant difference in hospital mortality between patients with VAP or VAT, and mortality in VAP patients was even lower than in VAT patients (19.3% vs 21.4% respectively, $p = 0.789$) [31]. An international survey found that half of physicians participated believed VAT could increase risk of mortality [28]. In our study, mortality in patients with other VARI was lower than in patients without VARI, although it did not reach statistically significant. The reason for lower rate of mortality in patients with other VARI could be due to heterogeneity of study population which masked real impact of VARI on mortality. In subgroup analysis in patients with sepsis & septic shock and tetanus, mortality with other VARI was higher than in patients without VARI (Table 6 – 9).

Mortality in patients with VARI was higher than in patients without VARI among each type of admission diagnosis categories, although these differences were not statistically significant. In a multivariate analysis adjusting for admission diagnosis and severity of disease, VARI status had similar impact on mortality as in univariate with no statistically significant effect (Table 6 – 13). Only increase in APACHE II score were statistically associated with mortality increase and tetanus patients had statistically lower risk for death in compared with CNS infection patients.

Melsen et al. in a systematic review found that there was no evidence for association between VAP and mortality in ARDS or trauma patients [171]. Mathai et al. conducted a prospective observational study at an adult ICU of a tertiary hospital in North India from 1st December 2010 to 30th November 2011 on adult patients ventilated for > 48 hours with total 250 patients enrolled, of which 95 patients developed VAP. Authors reported that there was no difference in mortality between patients with VAP and patients without VAP overall (68.4% vs 61.3%, respectively, $p = 0.200$), but patients with higher admission APACHE II scores had significantly higher mortality ($p = 0.010$) [46]. Arabi et al. in systematic review on VAP found that crude mortality in VAP patients ranged from 16% to 94% in compared with mortality of 0.2% to 51% in patients without VAP [48].

In our study, no significant difference in mortality between those with or without appropriate antibiotic therapy was found (Table 6 – 10). Inchai et al. found that early or late inappropriate initial antibiotics treatment was associated with higher risk for 30 day mortality in compared with early appropriate initial treatment, odds ratios (95% CI) were 2.05 (1.58 – 2.83), $p < 0.001$ and 1.96 (1.17 – 3.30), $p = 0.011$ respectively [51]. However, in multivariate analysis they found that early inappropriate initial treatment was not statistically higher risk for mortality, but late inappropriate initial treatment was statistically significant higher risk for death in compared with early appropriate treatment. Nihal Piskin et al. conducted a retrospective study at a tertiary hospital in Turkey from January 2005 to January 2008 on

initial antibiotics treatment of HAP and VAP [200]. Similar to our study they found no differences in 28-day mortality of patients with VAP who received adequate and inadequate initial treatment This could be explained by the fact that those with more severe condition when VARI diagnosed were more likely to receive active broad spectrum antibiotics. Therefore, these patients received adequate empiric antibiotics therapy. However, their more severity status leaded to their high mortality. Furthermore in our study, patients often already had a bacterial culture result before the decision to diagnose VAP and start antibiotics was made, therefore relatively few were treated with inappropriate antibiotics.

Conclusion

The majority of pathogens associated with VARI were *A. baumannii, P. aeruginosa,* and *K. pneumonia* with considerable high rate of carbapenems resistance. Not only VAP but also the other VARI resulted in nearly doubling the ICU stay, ventilation time, antibiotics consumption, and ICU cost compared with patients without VARI. Therefore, infection control practice should firstly focus on VARI to confine and decrease these huge issues and also risk of spread high antibiotics resistance bacteria to community. VARI did not showed significant impact on mortality. However VAP was associated with an increased risk of death at 28 days with an estimated attributable mortality of 10.3% in overall and 20.2% in subgroup of non-tetanus patients.

Chapter 7

General discussion and recommendations

At the time the work in this thesis was done there was no national surveillance system for hospital acquired infections in Vietnam. The little data available on HAI came from small number of tertiary hospitals and showed a high prevalence of HAI in ICUs with high proportion of the associated pathogens showing resistance to even the broadest spectrum antibiotics. These limited data suggested that the burden of HAI and antibiotic resistance in Vietnamese ICUs was high. However, more compelling, systematic and far reaching evidence on the prevalence of HAI, associated antibiotic resistance, and risk factors was needed to present to policy makers. The research in this thesis comprises the largest study exploring HAI in Vietnamese ICUs, with 3287 patients in 15 ICUs of 14 hospitals. These research activities have played an important part in raising awareness of HAI, overuse of antibiotics, and the antibiotic resistance situation in Vietnamese hospitals in general, and ICUs in particular. Furthermore, the hospitals involved in this work have become the core of a new national surveillance system for antibiotic resistance in Vietnam, established in May 2016.

The study, results detailed in chapters 3 & 4, confirmed the high prevalence of HAI in Vietnam ICUs, in average 29.5% of ICU patients was suffering from at least one HAI everyday with 80% of those HAIs was hospital acquired pneumonia. All invasive devices were associated with higher risk for HAI, e.g. intubation, central vascular catheterization, urinary catheterization, and even peripheral vascular catheter. The study found that a large proportion of HAI (31.6%) was acquired in another department before ICU admission, showing a need for interventions outside the ICU setting. All these factors should be targets to explore for HAI prevention programmes. Where there are locally applicable data to show that an intervention is likely to succeed in reducing HAI, that intervention should be explored and

evaluated. Where there is no locally relevant data, research is urgently needed to provide solutions.

The second study, results detailed in chapters 5 & 6, showed that VARI has substantial impact on patients, with increased ICU stays of 11 days on average (27 vs 16 days), increased ventilation duration of 12.5 days (21.5 vs 9 days), increased antibiotic consumption of 11 DOT/patient (28 vs 17 DOT/patient); and an increase in ICU cost of 2189 US$ (4723 vs 2534 US$) compared with patients without VARI.

Given an estimated 22,570 patients admitted to the ICUs of 14 surveyed hospitals in the year 2012 and VARI prevalence of 24.6% as in the second study, we would expect 5,552 patients developed VARI leading to an extra 69,403 ventilation days, 61,074 ICU days, 61,074 DOT antibiotic consumption, and 12,153,810 US$ ICU direct costs. With a total of 40 tertiary and 304 provincial acute care hospitals across Vietnam, the extra cost for VARI nationally would be many times higher and could account for a significant proportion of total health expenditure in 2012 (~ 4.7 billion US$) [101]. Clearly such a calculation is simplistic, and based on assumptions that may not be true, however it is clear that the cost of VARI even in simple financial terms is significant at a national level, highlighting the need for urgent action.

Hospital acquired pneumonia was by far the most common HAI reported (~ 80% of HAI). Given the limited resource in middle income countries such as Vietnam, this should be the first priority to resolve. Many measures have been implemented in high income countries, such as VAP bundles, new endotracheal tube designs (for example with subglottic suction ports and polyurethane cuffs), minimization of sedatives, and others. Differences in hospital and ICU infrastructure, medical equipment, staffing, infection control facilities bring into question whether these measures would have positive results in countries like Vietnam. Given the resource implications for most of these interventions, further studies to establish firm evidence are needed before expanding to national application.

These studies have also demonstrated the high level of antibiotic use in Vietnamese ICUs, both through the high proportion of patients on antibiotics (84.8%) and the high antibiotic consumption (average 173.7 DOT/100 PD) as detailed in chapter 4. This level of antibiotic consumption could be a result of the admissions having a high prevalence of infectious diseases, which was the reason for ICU admission for 46.3% patients in ICU. However, a more important factor is the high proportion of antibiotics used with no clear indication (overall 14.9%, up to 46.0% in an individual ICUs), suggesting widespread misuse. Antibiotic use is an important factor for the development of resistance to antibiotics [153]. In addition, the consumption of 23.9 and 5.7 DOT/100 PD respectively of the 'last resort' antibiotics carbapenems and colistin on average (rising to 81.9 and 66 DOT/100 PD in one ICU) is highly alarming. These data suggest that antibiotic stewardship is urgently needed to avoid inappropriate use of antibiotics. Currently few hospital ICUs have such programmes, and fewer still have active, daily input from infectious diseases or microbiology specialists into appropriate diagnostics and antibiotic prescribing.

The high prevalence of carbapenem resistance among HAI pathogens described is associated with the increased use of these last resort antibiotics. The high ESBL prevalence rate in Vietnam, drives the higher carbapenem consumption [206]. However, now we are reaching unacceptable high levels of carbapenem resistance, significantly diminishing our arsenal of effective drugs. Approaches to address this problem include exploring the use of alternatives to carbapenems where suitable (such as temocillin as an alternative treatment for ESBL producing Enterobacteriaceae) and strict infection control to limit spread of carbapenem resistant organisms within hospitals. With inadequate infrastructure and limited staff, simple measures (such as hand hygiene, cleaning and disinfection of the hospital environment) should be strictly implemented first. More complicated measures (e.g. changes to the infrastructure of hospital including provision of adequate side rooms, changes to systems that may encourage antibiotic use and investment in rapid diagnosis of highly resistant pathogens

to aid infection control) need to be evaluated carefully, including costs, before systematic application.

Additionally, actions to prevent or delay the development of antibiotic resistance also play an essential role. Antibiotic use is the most important condition for the evolution of antibiotic resistance. However, antibiotic use is essential for the treatment of infectious diseases. Therefore, appropriate use of antibiotics is especially important to limit antibiotic consumption. Inappropriate antibiotic use fuels the development of resistance without any benefit. Although not in the scope of this thesis, an understanding that hospitals and ICUs are not in isolation is needed. So addressing this inappropriate use of antibiotics requires measures applied not only to human health in hospitals and the community but also to agriculture. It requires systematic cooperation of many ministries including the Ministry of Health and Ministry of Agriculture and Rural Development in Vietnam.

In hospitals, two main types of measures are appropriate antibiotic use and effective infection prevention (infection control practice). To improve appropriate antibiotic use needs to develop national and institutional guidelines on diagnosis and treatment infectious diseases based on their current data on pathogen and antibiotic resistance, establish and enhance antibiotic stewardship programmes, monitoring and feedback on antibiotic use and antibiotic resistance. Ideally these data and if possible certain important bacteria, should be sent to a central national reference laboratory to continually monitor levels of resistance in important bacteria and assess whether policy interventions are having impact in control.

Infection control programmes need to be supplied adequate resources for efficient practice and will likely need new evidence to inform policies in these settings of high levels of resistance but limited resources and poor infrastructure for infection control purposes. A certainty is that as Vietnamese medical care improves, with more patients having complex surgeries, chemotherapy etc the burden of antibiotic resistance will become more severe.

There is certainly no little difficulty but these measures really could be done if there are active involvement of both government and community.

In conclusion, this thesis includes the largest point prevalence survey on hospital acquired infection and antimicrobial use in ICUs in Vietnam and an observational study on ventilator associated pneumonia and other ventilator associated respiratory infections. The thesis provides evidence of the high burden of HAI in Vietnam ICUs along with substantial impacts on ventilation duration, ICU stay, antibiotic use, and cost. In addition, the high proportion of carbapenems resistance among HAI pathogens is clear evidence for resources to enable the enhancement of infection control practice in Vietnamese ICUs.

Appendix A: Supplementary Tables

Table A – 1: Basic characteristics of participating hospitals and ICUs.

Hospital Code	Basic hospital information						Basic ICU information												
	Total bed	patients /year	patient days /year	Alcohol hand rub per year (litres)	Infection control		Type of ICU[a]	Patients No. /year	Patient days /year	Mean ICU stay (day)	Alcohol hand rub per year (litres)	Alcohol use per patient day (ml)	Total beds	No. Room	Single room	No. doctors	No. nurses	Doctor/ bed	Nurse/ Bed
					Nurses	Doctors													
H01	280	7,365	76,342	1,030	0	2	I-ICU	497	4,631	9.3	130	28.1	18	6	2	4	22	0.22	1.22
H02	1900	114,000	1,290,000	6,152	12	2	G-ICU	1,345	14,007	10.4	1,408	100.5	38	12	6	13	55	0.34	1.45
H04	841	42,074	287,323	400	4	2	M-ICU	1,240	5,904	4.8	140	16.9	20	4	0	7	25	0.35	1.25
							S-ICU	1,228	5,904	4.8	100	23.7	17	4	0	4	24	0.24	1.41
H05	1050	41,106	366,828	1,200	29	11	S-ICU	696	5,064	7.3	336	66.4	16	2	0	4	40	0.25	2.50
H06	900	41,430	356,356	3,500	0	1	M-ICU	1,052	5,704	5.4	500	87.7	16	5	0	11	24	0.69	1.50
H07	750	34,848	183,885	2,996	2	1	G-ICU	751	3,508	4.7	482	137.4	10	4	0	7	18	0.70	1.80
H08	1050	15,000	60,000	1,000	12	6	M-ICU	1,674	6,418	3.8	480	74.8	20	5	0	5	22	0.25	1.10
H09	1500	85,054	712,844	5640	25	1	G-ICU	3,049	20,772	6.8	2,210	106.4	47	7	0	13	38	0.28	0.81
H10	2362	85,608	891,908	10,500	10	2	M-ICU	2,530	16,280	6.4	1,200	73.7	60	7	6	11	66	0.18	1.10
H11	1000	57,523	373,910	650	6	0	M-ICU	2,356	12,323	5.2	480	39.0	34	1	0	15	48	0.44	1.41
H12	750	48,049	290,215	110	2	1	G-ICU	2,374	12,218	5.1	110	9.0	20	4	0	9	32	0.45	1.60
H13	1800	123,850	918,026	13,066	3	2	G-ICU	1,196	11,901	10.0	500	42.0	31	3	0	15	54	0.48	1.74
H15	550	41,751	288,696	1,113	3	1	I-ICU	540	8,651	16.0	900	104.0	23	5	1	8	48	0.35	2.09
H16	800	49,248	326,723	7,200	5	1	G-ICU	2,042	18,786	9.2	360	19.2	30	1	0	16	33	0.53	1.10

[a] I: infectious, G: general (mixed), M: medical, S: surgical.

Table A – 2: Patient Characteristics

Characteristics		Tertiary hospitals						Provincial hospitals									Total
Hospital code		**H01**	**H02**	**H05**	**H10**	**H13**	**H16**	**H04**	**H04**	**H06**	**H07**	**H08**	**H09**	**H11**	**H12**	**H15**	
ICU type		**I-ICU**	**G-ICU**	**S-ICU**	**G-ICU**	**G-ICU**	**G-ICU**	**S-ICU**	**M-ICU**	**M-ICU**	**G-ICU**	**M-ICU**	**G-ICU**	**M-ICU**	**G-ICU**	**I-ICU**	
No. patients, n		**203**	**223**	**138**	**578**	**277**	**214**	**89**	**54**	**148**	**145**	**187**	**403**	**223**	**223**	**182**	**3287**
Age (years)	Mean (median, IQR)	52.5 (53, 43 – 65)	54.7 (57, 39 – 71)	47.5 (47, 27 – 64.2)	56.5 (56, 40 – 76)	59.6 (64, 44 – 76)	68.3 (72, 57.7 – 83)	54.1 (57, 38 – 70)	70.7 (73, 62 – 81)	65.8 (68, 54.5 – 79.7)	59.2 (64, 45.5 – 76)	67.3 (73, 53 – 79)	64.5 (68, 50 – 80)	60.8 (63, 48 – 78)	57.8 (59, 37 – 80)	51.9 (54, 35 – 65)	59.2 (61, 45 – 77)
	Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Gender, n (%)	Male	145 (71.4)	145 (65)	111 (80.4)	415 (71.8)	145 (52.3)	111 (51.9)	61 (68.5)	31 (57.4)	96 (64.9)	114 (78.6)	118 (63.1)	210 (52.1)	138 (61.9)	143 (64.1)	118 (64.8)	2101(63.9)
	Female	58 (28.6)	78 (35)	27 (19.6)	163 (28.2)	132 (47.7)	103 (48.1)	28 (31.5)	23 (42.6)	52 (35.1)	31 (21.4)	69 (36.9)	193 (47.9)	85 (38.1)	80 (35.9)	64 (35.2)	1186(36.1)
	Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Comorbidity, n (%)	Yes	82 (40.6)	131 (59.5)	8 (5.8)	107 (18.5)	121 (43.7)	126 (59.1)	28 (31.5)	34 (63)	104 (70.3)	87 (60)	93 (49.7)	141 (37)	43 (36.4)	83 (37.2)	61(30.1)	1249(39.6)
	No	120 (59.4)	89 (40.5)	129 (94.2)	471 (81.5)	156 (56.3)	87 (40.9)	61 (68.5)	20 (37)	44 (29.7)	58 (40)	94 (50.3)	240 (63)	75 (63.6)	140 (62.8)	118 (69.9)	1902(60.4)
	Missing	1	3	1	0	0	1	0	0	0	0	0	22	105	0	3	136
Source of ICU admission, n (%)	Commu_ nity	0	59 (26.8)	10 (10.1)	424 (73.4)	19 (6.9)	79 (36.9)	26 (29.2)	47 (87)	99 (67.3)	78 (53.8)	102 (54.5)	207 (53.6)	23 (28.7)	197 (89.1)	57 (31.8)	1427(46.2)
	Current hospital	115 (57.2)	85 (38.6)	94 (85.5)	90 (15.6)	159 (57.4)	66 (30.8)	27 (30.3)	3 (5.6)	37 (25.2)	40 (27.6)	45 (24.1)	101 (26.2)	32 (40)	16 (7.2)	20 (11.2)	930 (30.1)
	Other hospital	86 (42.8)	76 (34.5)	6 (5.5)	64 (11.1)	96 (34.7)	69 (32.2)	22 (24.7)	3 (5.6)	8 (5.4)	27 (18.6)	40 (21.4)	26 (6.7)	8 (10)	6 (2.7)	101 (56.4)	638 (20.7)
	Other	0	0	0	0	3 (1.1)	0	14 (15.7)	1 (1.9)	3 (2.0)	0	0	52 (13.5)	17 (21.3)	2 (0.9)	1 (0.6)	93 (3)
	Missing	2	3	28	0	0	0	0	0	1	0	0	17	143	2	3	199
Reason for admission, n (%)	Medical	1 (0.5)	82 (37.3)	3 (2.8)	368 (63.7)	32 (11.6)	100 (46.7)	11 (12.6)	31 (57.4)	99 (68.3)	57 (39.3)	46 (24.7)	189 (49.7)	42 (52.5)	139 (63.2)	3 (1.7)	1203(39.1)
	Infection	200 (99.5)	123 (55.9)	6 (5.5)	88 (15.2)	159 (57.4)	114 (53.3)	13 (14.9)	23 (42.6)	46 (31.7)	37 (25.5)	140 (75.3)	188 (49.5)	31 (38.8)	81 (36.8)	174 (97.8)	1423(46.3)
	Surgery	0	15 (6.8)	100 (91.7)	122 (21.1)	86 (31)	0	63 (72.4)	0	0	51 (35.2)	0	3 (0.8)	7 (8.8)	0	1 (0.6)	448 (14.6)
	Missing	2	3	29	0	0	0	2	0	3	0	1	23	143	3	4	213
Surgery since admission, n (%)	None	118 (58.1)	160 (72.7)	4 (2.9)	541 (93.6)	127 (45.8)	156 (72.9)	28 (31.5)	52 (96.3)	136 (91.9)	94 (64.8)	186 (99.5)	375 (93.1)	154 (69.1)	218 (97.8)	121 (66.5)	2470(75.2)
	Minor	85 (41.9)	31 (14.1)	0	3 (0.5)	43 (15.5)	29 (13.6)	3 (3.4)	1 (1.9)	9 (6.1)	5 (3.4)	1 (0.5)	9 (2.2)	45 (20.2)	2 (0.9)	61 (33.5)	327 (10)
	Major	0	29 (13.2)	134 (97.1)	34 (5.9)	107 (38.6)	29 (13.6)	58 (65.2)	1 (1.9)	3 (2.0)	46 (31.7)	0	19 (4.7)	24 (10.8)	3 (1.3)	0	487 (14.8)
	Missing	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	3

Characteristics		Tertiary hospitals						Provincial hospitals									Total
Hospital code		**H01**	**H02**	**H05**	**H10**	**H13**	**H16**	**H04**	**H04**	**H06**	**H07**	**H08**	**H09**	**H11**	**H12**	**H15**	
ICU type		**I-ICU**	**G-ICU**	**S-ICU**	**G-ICU**	**G-ICU**	**G-ICU**	**S-ICU**	**M-ICU**	**M-ICU**	**G-ICU**	**M-ICU**	**G-ICU**	**M-ICU**	**G-ICU**	**I-ICU**	
No. patients, n		**203**	**223**	**138**	**578**	**277**	**214**	**89**	**54**	**148**	**145**	**187**	**403**	**223**	**223**	**182**	**3287**
Intubation, n (%)	Yes	165 (81.3)	98 (43.9)	138 (100)	184 (31.8)	241 (87)	160 (74.8)	45 (50.6)	7 (13)	76 (51.4)	81 (55.9)	117 (62.6)	189 (46.9)	92 (41.3)	50 (22.4)	76 (41.8)	1719(52.3)
	No	38 (18.7)	125 (56.1)	0	394 (68.2)	36 (13)	54 (25.2)	44 (49.4)	47 (87)	72 (48.6)	64 (44.1)	70 (37.4)	214 (53.1)	131 (58.7)	173 (77.6)	106 (58.2)	1568(47.7)
	Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Central vascular catheter, n (%)	Yes	99 (48.8)	129 (57.9)	133 (96.4)	49 (8.5)	213 (76.9)	31 (14.5)	44 (49.4)	3 (5.6)	38 (25.7)	13 (9)	7 (3.7)	79 (19.6)	17 (7.6)	31 (13.9)	35 (19.2)	921 (28)
	No	104 (51.2)	94 (42.1)	5 (3.6)	529 (91.5)	64 (23.1)	183 (85.5)	45 (50.6)	51 (94.4)	110 (74.3)	132 (91)	180 (96.3)	324 (80.4)	206 (92.4)	192 (86.1)	147 (80.8)	2366 (72)
	Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Urinary catheter, n (%)	Yes	170 (83.7)	133 (59.6)	137 (99.3)	71 (12.3)	246 (88.8)	107 (50)	69 (77.5)	11 (20.4)	51 (34.5)	65 (44.8)	33 (17.6)	265 (65.8)	68 (30.5)	128 (57.4)	62 (34.1)	1616(49.2)
	No	33 (16.3)	90 (40.4)	1 (0.7)	507 (87.7)	31 (11.2)	107 (50)	20 (22.5)	43 (79.6)	97 (65.5)	80 (55.2)	154 (82.4)	138 (34.2)	155 (69.5)	95 (42.6)	120 (65.9)	1671(50.8)
	Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Peripheral vascular catheter, n (%)	Yes	126 (62.1)	188 (84.3)	5 (3.6)	532 (92)	182 (65.7)	213 (99.5)	67 (75.3)	45 (83.3)	100 (67.6)	106 (73.1)	169 (90.4)	391 (97)	216 (96.9)	217 (97.3)	166 (91.2)	2723(82.8)
	No	77 (37.9)	35 (15.7)	133 (96.4)	46 (8)	95 (34.3)	1 (0.5)	22 (24.7)	9 (17.6)	48 (32.4)	39 (26.9)	18 (9.6)	12 (3)	7 (3.1)	6 (2.7)	16 (8.8)	564 (17.2)
	Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dialysis, n (%)	Yes	13 (6.4)	75 (33.6)	0	4 (0.7)	57 (20.6)	25 (11.7)	0	0	19 (12.8)	9 (6.2)	2 (1.1)	21 (5.2)	34 (15.2)	7 (3.1)	4 (2.2)	270 (82)
	No	190 (93.6)	148 (66.4)	138 (100)	574 (99.3)	220 (79.4)	189 (88.3)	89 (100)	54 (100)	129 (87.2)	136 (93.8)	185 (98.9)	382 (94.8)	189 (84.8)	216 (96.9)	178 (97.8)	3017(91.8)
	Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Family support in patient care, n (%)	Yes	198 (97.5	220 (98.7)	2 (1.4)	573 (99.1)	6 (2.2)	2 (0.9)	89 (100)	54 (100)	148 (100)	142 (97.9)	187 (100)	5 (1.2)	222 (99.6)	221 (99.1)	3 (1.6)	2072(63.0)
	No	5 (2.5)	3 (1.3)	136 (98.6)	5 (0.9)	271 (97.8)	212 (99.1)	0	0	0	3(2.1)	0	398 (98.8)	1 (0.4)	2 (0.9)	179 (98.4)	1215(37.0)
Antibiotic use, n (%)	Yes	155 (76.4)	184 (82.5)	134 (97.1)	577 (99.8)	250 (90.3)	175 (81.8)	83 (93.3)	27 (50)	131 (88.5)	89 (61.4)	148 (79.1)	383 (95)	188 (84.3)	136 (61)	127 (69.8)	2787(84.8)
	No	48 (23.6)	39 (17.5)	4 (2.9)	1 (0.2)	27 (9.7)	39 (18.2)	6 (6.7)	27 (50)	17 (11.5)	56 (38.6)	39 (20.9)	20 (5)	35 (15.7)	87 (39)	55 (30.2)	500 (15.2)
	Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hospital acquired infection, n (%)	Yes	68 (33.5)	84 (38.5)	84 (60.9)	40 (6.9)	140 (50.5)	126 (59.2)	12 (13.5)	3 (5.6)	43 (30.5)	21 (14.5)	40 (21.4)	146 (36.8)	81 (36.5)	36 (16.1)	41 (22.7)	965 (29.5)
	No	135 (66.5)	134 (61.5)	54 (39.1)	538 (93.1)	137 (49.5)	87 (40.8)	77 (86.5)	51 (94.4)	98 (69.5)	124 (85.5)	147 (78.6)	251 (63.2)	141 (63.5)	187 (83.9)	140 (77.3)	2301(70.5)
	Missing	0	5	0	0	0	1	0	0	7	0	0	6	1	0	1	21

Table A – 3: Antimicrobials Combinations

combination of 2 antimicrobials			combination of 3 antimicrobials				Combination of 4 antimicrobials				
Antimicrobial combinations (n = 1343)		% (n)	Antimicrobial combinations (n = 552)			% (n)	Antimicrobial combinations (n=159)				% (n)
J01DD Third-generation cephalosporins	J01MA Fluoroquinolones	19.1 (257)	J01DD Third-generation cephalosporins	J01MA Fluoroquinolones	J01XA Glycopeptide antibacterials	13.6 (75)	J01DE Fourth-generation cephalosporins	J01GB Other aminoglycosides	J01MA Fluoroquinolones	J01XA Glycopeptide antibacterials	13.2 (21)
J01DH Carbapenems	J01MA Fluoroquinolones	10.8 (145)	J01DD Third-generation cephalosporins	J01MA Fluoroquinolones	J01XD Imidazole derivatives	6.0 (33)	J01DD Third-generation cephalosporins	J01GB Other aminoglycosides	J01MA Fluoroquinolones	J01XA Glycopeptide antibacterials	10.7 (17)
J01DD Third-generation cephalosporins	J01GB Other aminoglycosides	7.8 (105)	J01DH Carbapenems	J01MA Fluoroquinolones	J01XA Glycopeptide antibacterials	6.0 (33)	J01CR Combinations of penicillins included beta-lactamase inhibitors	J01DD Third-generation cephalosporins	J01MA Fluoroquinolones	J01XA Glycopeptide antibacterials	3.1 (5)
J01DH Carbapenems	J01XA Glycopeptide antibacterials	5.0 (67)	J01DD Third-generation cephalosporins	J01GB Other aminoglycosides	J01MA Fluoroquinolones	5.6 (31)	J01DC Second-generation cephalosporins	J01GB Other aminoglycosides	J01MA Fluoroquinolones	J01XA Glycopeptide antibacterials	2.5 (4)
J01DE Fourth-generation cephalosporins	J01MA Fluoroquinolones	4.8 (65)	J01DE Fourth-generation cephalosporins	J01MA Fluoroquinolones	J01XA Glycopeptide antibacterials	4.9 (27)	J01DD Third-generation cephalosporins	J01FA Macrolides	J01MA Fluoroquinolones	J01XA Glycopeptide antibacterials	2.5 (4)
J01DH Carbapenems	J01XB Polymyxins (colistin injection)	4.5 (61)	J01DD Third-generation cephalosporins	J01GB Other aminoglycosides	J01XA Glycopeptide antibacterials	2.9 (16)	J01DD Third-generation cephalosporins	J01MA Fluoroquinolones	J01XA Glycopeptide antibacterials	J01XD Imidazole derivatives	2.5 (4)
J01DH Carbapenems	J01XD Imidazole derivatives	4.4 (59)	J01DE Fourth-generation cephalosporins	J01GB Other aminoglycosides	J01MA Fluoroquinolones	2.5 (14)	J01DH Carbapenems	J01GB Other aminoglycosides	J01MA Fluoroquinolones	J01XA Glycopeptide antibacterials	2.5 (4)
J01DD Third-generation cephalosporins	J01XD Imidazole derivatives	4.2 (57)	J01DH Carbapenems	J01MA Fluoroquinolones	J01XD Imidazole derivatives	2.5 (14)	J01CR Combinations of penicillins included beta-lactamase inhibitors	J01DE Fourth-generation cephalosporins	J01FA Macrolides	J01MA Fluoroquinolones	1.9 (3)
J01DH Carbapenems	J01XX Other antibacterials	3.4 (46)	J01DH Carbapenems	J01XA Glycopeptide antibacterials	J01XD Imidazole derivatives	2.2 (12)	J01CR Combinations of penicillins included beta-lactamase inhibitors	J01DE Fourth-generation cephalosporins	J01MA Fluoroquinolones	J01XA Glycopeptide antibacterials	1.9 (3)
J01DH Carbapenems	J01GB Other aminoglycosides	2.8 (38)	J01DH Carbapenems	J01XA Glycopeptide antibacterials	J01XB Polymyxins	2.0 (11)	J01DE Fourth-generation cephalosporins	J01FA Macrolides	J01GB Other aminoglycosides	J01XA Glycopeptide antibacterials	1.9 (3)
Other 91 combinations		33.0 (443)	Other 137 combinations			51.8 (286)	Other 77 combinations				57.2 (97)

Table A – 4: The Common Antimicrobial Agents Used

Patients used two antimicrobials (n = 1343 patient)		Patients used three antimicrobials (n = 552 patients)		Patients used four antimicrobials (n = 159 patients)		Total antimicrobials used (n=5590)	
Antimicrobial group	% (n)	Antimicrobial group	% (n)	Antimicrobial group	% (n)	Antimicrobial group	% (n)
J01MA Fluoroquinolones	21.1 (556)	J01MA Fluoroquinolones	21.1 (350)	J01MA Fluoroquinolones	19.3 (123)	J01DD Third-generation cephalosporins	20.1 (1126)
J01DD Third-generation cephalosporins	19.8 (533)	J01XA Glycopeptide antibacterials	15.5 (257)	J01XA Glycopeptide antibacterials	17.3 (110)	J01MA Fluoroquinolones	19.4 (1082)
J01DH Carbapenems	16.6 (445)	J01DD Third-generation cephalosporins	13.6 (225)	J01GB Other aminoglycosides	15.1 (96)	J01DH Carbapenems	14.1 (786)
J01GB Other aminoglycosides	9.2 (247)	J01GB Other aminoglycosides	10.3 (171)	J01DD Third-generation cephalosporins	8.8 (56)	J01XA Glycopeptide antibacterials	9.6 (536)
J01XA Glycopeptide antibacterials	5.7 (153)	J01DH Carbapenems	10.3 (170)	J01DE Fourth-generation cephalosporins	8.6 (55)	J01GB Other aminoglycosides	9.3 (521)
J01XD Imidazole derivatives	5.5 (149)	J01XD Imidazole derivatives	6.4 (106)	J01DH Carbapenems	5.8 (37)	J01DE Fourth-generation cephalosporins	5.5 (310)
J01DE Fourth-generation cephalosporins	4.4 (118)	J01DE Fourth-generation cephalosporins	5.3 (87)	J01XD Imidazole derivatives	4.6 (29)	J01XD Imidazole derivatives	5.2 (289)
J01XB Polymyxins	4.2 (112)	J01XB Polymyxins	3.6 (60)	J01FA Macrolides	3.9 (25)	J01CR Combinations of penicillins included beta-lactamase inhibitors	3.5 (194)
J01CR Combinations of penicillins included beta-lactamase inhibitors	3.3 (88)	J01CR Combinations of penicillins included beta-lactamase inhibitors	1.8 (29)	J01CR Combinations of penicillins included beta-lactamase inhibitors	3.3 (21)	J01XB Polymyxins	3.3 (186)
J01XX Other antibacterials	3.1 (83)	J01DC Second-generation cephalosporins	1.7 (28)	J01DC Second-generation cephalosporins	2.8 (18)	J01XX Other antibacterials	2.2 (122)
18 other antibacterial groups	7.1 (192)	18 other antibacterial groups	10.4 (173)	16 other 16 antibacterial groups	10.4 (66)	12 other antibacterial groups	7.8 (438)

Table A – 5: Antimicrobials resistance of pathogens for HAIs originated from surveyed hospitals

Antimicrobial resistance of isolates	Tertiary ICUs						Provincial ICUs								Total
	H01	H02	H05	H10	H13	H16	H04	H06	H07	H08	H09	H11	H12	H15	
Total isolates with susceptibility available	51	37	117	22	91	50	2	21	16	40	67	27	17	34	592
K. pneumoniae C3-R, % (C3-R/isolates)	50.0 (5/10)	100.0 (3/3)	66.7 (6/9)	100.0 (5/5)	75.0 (3/4)	81.8 (9/11)	0.0 (0/0)	50.0 (1/2)	0.0 (0/0)	0.0 (0/2)	81.8 (9/11)	100.0 (2/2)	100.0 (3/3)	16.7 (1/6)	69.1 (47/68)
K. pneumoniae Car-R, % (n/isolates)	10.0 (1/10)	33.3 (1/3)	11.1 (1/9)	0.0 (0/5)	25.0 (1/4)	18.2 (2/11)	0.0 (0/0)	0.0 (0/2)	0.0 (0/0)	0.0 (0/2)	27.3 (3/11)	50.0 (1/2)	0.0 (0/3)	0.0 (0/6)	14.7 (10/68)
Klebsiella spp. C3-R, % (n/isolates)	66.7 (2/3)	100.0 (1/1)	77.8 (7/9)	50.0 (2/4)	16.7 (1/6)	100.0 (2/2)	0.0 (0/0)	50.0 (1/2)	100.0 (1/1)	66.7 (2/3)	77.8 (7/9)	66.7 (4/6)	100.0 (2/2)	0.0 (0/0)	66.7 (32/48)
Klebsiella spp. Car-R, % (n/isolates)	33.3 (1/3)	0.0 (0/1)	11.1 (1/9)	0.0 (0/4)	0.0 (0/6)	0.0 (0/2)	0.0 (0/0)	0.0 (0/2)	0.0 (0/1)	0.0 (0/3)	0.0 (0/9)	16.7 (1/6)	0.0 (0/2)	0.0 (0/0)	6.3 (3/48)
E. coli C3-R, % (n/isolates)	100.0 (2/2)	80.0 (4/5)	33.3 (1/3)	100.0 (1/1)	0.0 (0/2)	33.3 (1/3)	0.0 (0/0)	0.0 (0/2)	100.0 (1/1)	33.3 (1/3)	75.0 (3/4)	75.0 (3/4)	0.0 (0/0)	66.7 (2/3)	57.6 (19/33)
E. coli Car-R, % (n/isolates)	0.0 (0/2)	40.0 (2/5)	0.0 (0/3)	0.0 (0/1)	0.0 (0/2)	0.0 (0/3)	0.0 (0/0)	0.0 (0/2)	0.0 (0/1)	0.0 (0/3)	0.0 (0/4)	0.0 (0/4)	0.0 (0/0)	0.0 (0/3)	6.1 (2/33)
Other Enterobacteriaceae C3-R, % (n/isolates)	44.4 (4/9)	0.0 (0/1)	72.2 (13/18)	0.0 (0/0)	40.0 (2/5)	100.0 (2/2)	100.0 (1/1)	0.0 (0/1)	50.0 (2/4)	60.0 (3/5)	75.0 (3/4)	100.0 (7/7)	0.0 (0/0)	0.0 (0/0)	64.9 (37/57)
Other Enterobacteriaceae Car-R, % (n/isolates)	0.0 (0/9)	0.0 (0/1)	11.1 (2/18)	0.0 (0/0)	0.0 (0/5)	50.0 (1/2)	100.0 (1/1)	0.0 (0/1)	0.0 (0/4)	0.0 (0/5)	0.0 (0/4)	0.0 (0/7)	0.0 (0/0)	0.0 (0/0)	7.0 (4/57)
Total Enterobacteriaceae C3-R, % (n/isolates)	54.2 (13/24)	80.0 (8/10)	69.2 (27/39)	80.0 (8/10)	35.3 (6/17)	77.8 (14/18)	100.0 (1/1)	28.6 (2/7)	66.7 (4/6)	50.0 (6/12)	78.6 (22/28)	84.2 (16/19)	100.0 (5/5)	33.3 (3/9)	65.5 (135/206)
Total Enterobacteriaceae Car-R, % (n/isolates)	8.3 (2/24)	30.0 (3/10)	10.3 (4/39)	20.0 (2/10)	5.9 (1/17)	16.7 (3/18)	100.0 (1/1)	0.0 (0/7)	0.0 (0/6)	0.0 (0/12)	10.7 (3/28)	10.5 (2/19)	0.0 (0/5)	0.0 (0/9)	9.2 (19/206)
A. baumannii Car-R, % (n/isolates)	94.1 (16/17)	100.0 (20/20)	100.0 (18/18)	100.0 (7/7)	97.8 (44/45)	100.0 (13/13)	0.0 (0/0)	25.0 (1/4)	0.0 (0/0)	20.0 (1/5)	73.3 (11/15)	50.0 (1/2)	33.3 (1/3)	83.3 (5/6)	89.0 (138/155)
Acinetobacter spp Car-R, % (n/isolates)	0.0 (0/1)	0.0 (0/0)	95.7 (22/23)	0.0 (0/0)	0.0 (0/0)	0.0 (0/0)	0.0 (0/0)	0.0 (0/0)	0.0 (0/0)	37.5 (3/8)	0.0 (0/1)	100.0 (3/3)	0.0 (0/0)	75.0 (6/8)	77.3 (34/44)
P. aeruginosa Car-R, % (n/isolates)	71.4 (5/7)	100.0 (4/4)	64.3 (9/14)	66.7 (2/3)	71.4 (5/7)	33.3 (2/6)	0.0 (0/0)	25.0 (1/4)	28.6 (2/7)	36.4 (4/11)	83.3 (5/6)	0.0 (0/0)	14.2 (1/7)	0.0 (0/2)	51.9 (41/79)
Methicillin resistant *S. aureus*, % (n/isolates)	0.0 (0/1)	100.0 (1/1)	100.0 (4/4)	0.0 (0/0)	85.7 (6/7)	87.5 (7/8)	0.0 (0/0)	0.0 (0/1)	100.0 (2/2)	100.0 (2/2)	25.0 (1/4)	100.0 (2/2)	0.0 (0/0)	100.0 (3/3)	77.8 (28/36)
Enterococcus spp. Glyco-R, % (n/isolates)	0.0 (0/0)	100.0 (1/1)	42.9 (3/7)	0.0 (0/0)	33.3 (2/6)	0.0 (0/0)	0.0 (0/0)	0.0 (0/0)	0.0 (0/0)	100.0 (1/1)	100.0 (4/4)	0.0 (0/0)	0.0 (0/0)	75.0 (3/4)	60.9 (14/23)

C3-R: resistant to 3rd generation cephalosporins, Car-R: resistant to carbapenems, Glyco-R: resistant to glycopeptides

Table A – 6: Antibiotics use for patients with carbapenem resistance pathogens

Combination with polymyxins (n =117)			Combination without polymyxins (n = 94)			Mono therapy (n = 30)		
Antibiotic agents	N	% AB use (n = 158)	Antibiotic agents	N	% AB use (n = 224)	Antibiotic agents	N	% AB use (n = 30)
Meropenem	33	20.9%	Meropenem	29	12.9%	Polymyxins	11	36.7%
Imipenem and enzyme inhibitor	29	18.4%	Vancomycin (parenteral)	27	12.1%	Cefoperazone, combinations	4	13.3%
Cefoperazone, combinations	24	15.2%	Imipenem and enzyme inhibitor	25	11.2%	Imipenem and enzyme inhibitor	3	10.0%
Vancomycin (parenteral)	24	15.2%	Levofloxacin	24	10.7%	Ampicillin and enzyme inhibitor	2	6.7%
Piperacillin and enzyme inhibitor	8	5.1%	Cefoperazone, combinations	22	9.8%	Fosfomycin	2	6.7%
Levofloxacin	7	4.4%	Fosfomycin	15	6.7%	Meropenem	2	6.7%
Amikacin	5	3.2%	Amikacin	13	5.8%	Cefepime	1	3.3%
Ampicillin and enzyme inhibitor	4	2.5%	Ciprofloxacin	9	4.0%	Ceftazidime	1	3.3%
Ciprofloxacin	3	1.9%	Doxycycline	8	3.6%	Ceftriaxone	1	3.3%
Doxycycline	3	1.9%	Metronidazole (parenteral)	6	2.7%	Ciprofloxacin	1	3.3%
Fosfomycin	3	1.9%	Netilmicin	6	2.7%	Gentamicin	1	3.3%
Netilmicin	3	1.9%	Piperacillin and enzyme inhibitor	6	2.7%	Piperacillin and enzyme inhibitor	1	3.3%
Cefepime	2	1.3%	Ceftazidime	5	2.2%			
Sulfamethoxazole and trimethoprim	2	1.3%	Cefepime	3	1.3%			
Teicoplanin	2	1.3%	Ceftriaxone	3	1.3%			
Ceftazidime	1	0.6%	Rifampicin	3	1.3%			
Doripenem	1	0.6%	Ampicillin and enzyme inhibitor	2	0.9%			
Metronidazole (parenteral)	1	0.6%	Clindamycin	2	0.9%			
Moxifloxacin	1	0.6%	Moxifloxacin	2	0.9%			
Rifampicin	1	0.6%	Sulfamethoxazole and trimethoprim	2	0.9%			
Trimethoprim	1	0.6%	The other antibiotics	12	5.4%			

Appendix B: Clinical Research Forms

B - 1: Clinical Research Forms for the Point Prevalence Survey

1. Hospital baseline form

VINA RES

HOSPITAL FORM - BASELINE

Instruction: This form is filled in for the whole hospital at the beginning of the project

Hospital code : _____

Survey date: _____ / _____ / 20_____ *(dd/mm/20yy)*

Hospital size (total number of beds): _____

Number of acute care beds: _____

Number of ICU beds (add all included ICUs together): _____

Hospital type:

O Primary

O Secondary

O Tertiary

O Specialized; Please indicate specialization: _____

	Number	Year data collected
Number of admissions in year		
Number of patient days in year		
Alcoholic hand rub consumption liters/year		
Number of patient rooms in hospital		
Number of single patient rooms in hospital		
Number of infection control nurses directly involved in patient care		
Number of infection control doctors		

2. ICU baseline form

VINA RES

ICU FORM – BASELINE

Instruction: This form is filled in for the ICU at the beginning of the project

Hospital code: _____

ICU name: _____

Survey date: _____ / _____ / 20_____ (*dd/mm/20yy*)

Antibiotic policy

Are there written guidelines regarding choice of antibiotic in the ICU?

O No O Yes → if yes: are they based on local antibiotic resistance surveillance O No O Yes

→ if yes: are they updated O Once a year O Less then once a year O Never

Is there a consultant/referent available to ask advice regarding antibiotics?

O Yes O No

Is re-evaluation* of antibiotic treatment perfomed?

O Routinely** O Sometimes O Never

*Re-evaluation of antibiotic treatment is defined as considering change, de-escalation or ceasing antibiotic treatment

**Routinely is defined as scheduled re-evaluation of antibiotic treatment after a specified duration of e.g. three days of treatment.

Infection Control

Are there alcohol based hand disinfection facilities in the ICU?

No O Yes → if yes: are they at each bed O No O Yes

Are visiting family members actively involved in patient care?

No O Yes → if yes: is it for O <50% of patients O 50-75% of patients O >75% of patients

→ if yes: are they educated about the importance of infection control O No O Yes

Is risk scoring used to assess patients?

O No O Yes → O Apache II O Apache III O SAPS 2 O SAPS 3 O Other _____

O Average risk score:_____

O Observed mortality (%) including patients taken home to die_____

Cultures

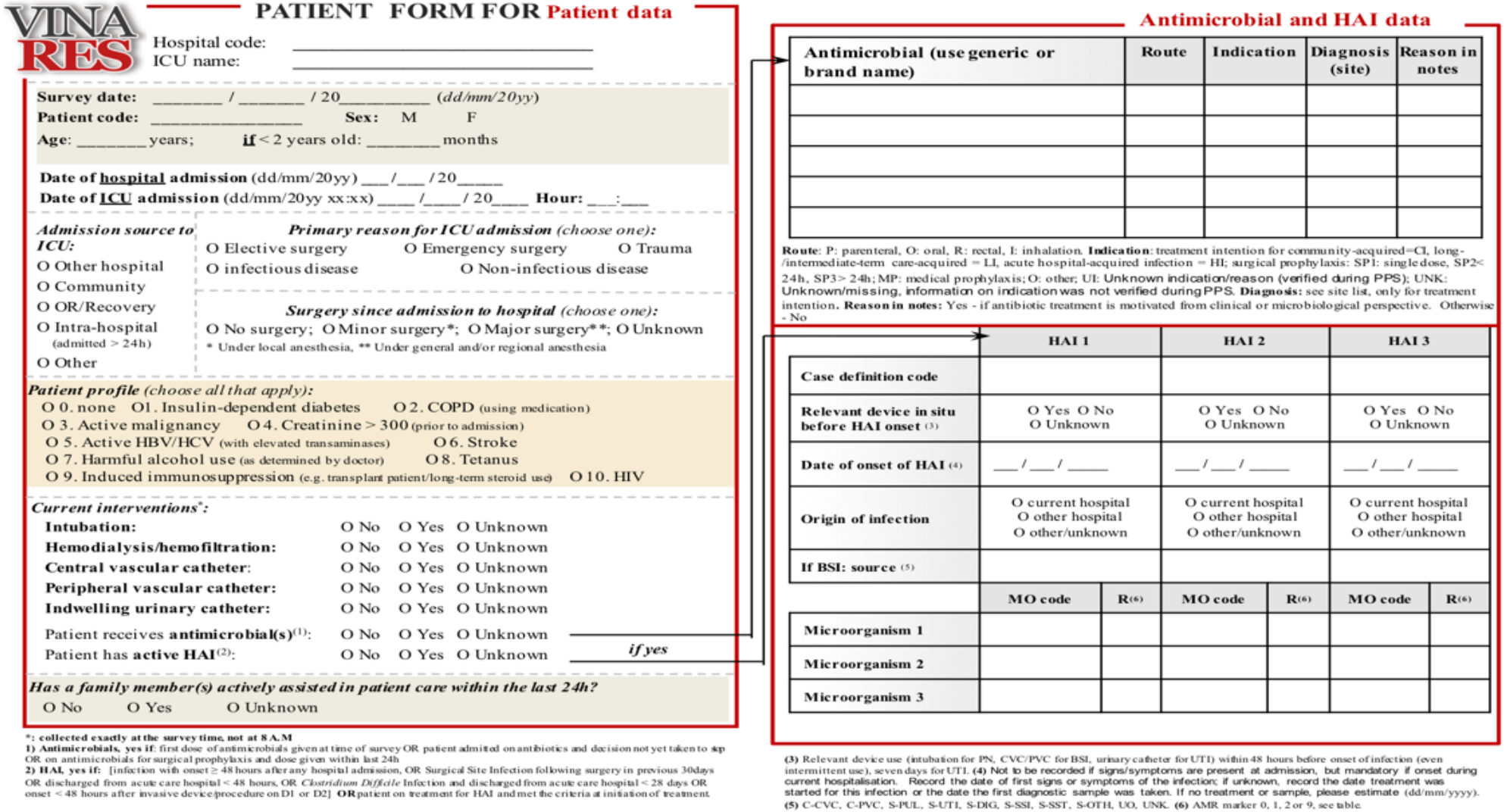
Are respiratory colonization ("surveillance") cultures taken from intubated patients at least once a week?

O Yes O No

Staff coverage	Number	Year data collected
Number of admissions in year		
Number of patient days in year		
Alcoholic hand rub consumption liters/year		
Number of patient beds		
Number of patient rooms		
Number of single patient rooms		
Number of intensive care doctors		
Number of intensive care nurses and nurse aids		

Screening of ARB's on patients				**Precautions for patient groups**		
Which pathogens do you screen for?				Isolation (single room or cohort care)	Standard precautions	Decontamination of patients
	All admission all the time	All admissions during outbreak	Selected high risk patients			
MRSA						
Enterobacteriace - ESBL						
Enterobacteriace - CarbapenemR						
VRE						
P. Aeruginosa - CarbapenemR						
A. Baumannii - CarbapenemR						

3. Patient form



PATIENT FORM FOR Patient data

VINA RES

Hospital code: _____
ICU name: _____

Survey date: _____ / _____ / 20_____ (*dd/mm/20yy*)
Patient code: _____ **Sex:** M F
Age: _____ years; **if** < 2 years old: _____ months

Date of hospital admission (dd/mm/20yy) ___/___/20____
Date of ICU admission (dd/mm/20yy xx:xx) ____/____/20____ **Hour:** ___:___

Admission source to ICU:
O Other hospital
O Community
O OR/Recovery
O Intra-hospital (admitted > 24h)
O Other

Primary reason for ICU admission *(choose one):*
O Elective surgery O Emergency surgery O Trauma
O infectious disease O Non-infectious disease

Surgery since admission to hospital *(choose one):*
O No surgery; O Minor surgery*; O Major surgery**; O Unknown
* Under local anesthesia, ** Under general and/or regional anesthesia

Patient profile *(choose all that apply):*
O 0. none O1. Insulin-dependent diabetes O 2. COPD (using medication)
O 3. Active malignancy O 4. Creatinine > 300 (prior to admission)
O 5. Active HBV/HCV (with elevated transaminases) O 6. Stroke
O 7. Harmful alcohol use (as determined by doctor) O 8. Tetanus
O 9. Induced immunosuppression (e.g. transplant patient/long-term steroid use) O 10. HIV

Current interventions*:

Intubation:	O No	O Yes	O Unknown	
Hemodialysis/hemofiltration:	O No	O Yes	O Unknown	
Central vascular catheter:	O No	O Yes	O Unknown	
Peripheral vascular catheter:	O No	O Yes	O Unknown	
Indwelling urinary catheter:	O No	O Yes	O Unknown	
Patient receives **antimicrobial(s)**(1):	O No	O Yes	O Unknown	*if yes*
Patient has **active HAI**(2):	O No	O Yes	O Unknown	

Has a family member(s) actively assisted in patient care within the last 24h?
O No O Yes O Unknown

*: **collected exactly at the survey time, not at 8 A.M**
1) Antimicrobials, yes if: first dose of antimicrobials given at time of survey OR patient admitted on antibiotics and decision not yet taken to stop OR on antimicrobials for surgical prophylaxis and dose given within last 24h
2) HAI, yes if: [infection with onset ≥ 48 hours after any hospital admission, OR Surgical Site Infection following surgery in previous 30days OR discharged from acute care hospital < 48 hours, OR *Clostridium Difficile* Infection and discharged from acute care hospital < 28 days OR onset < 48 hours after invasive device/procedure on D1 or D2] **OR** patient on treatment for HAI and met the criteria at initiation of treatment

Antimicrobial and HAI data

Antimicrobial (use generic or brand name)	Route	Indication	Diagnosis (site)	Reason in notes

Route: P: parenteral, O: oral, R: rectal, I: inhalation. **Indication**: treatment intention for community-acquired=CI, long-/intermediate-term care-acquired = LI, acute hospital-acquired infection = HI; surgical prophylaxis: SP1: single dose, SP2< 24h, SP3> 24h; MP: medical prophylaxis; O: other; UI: Unknown indication/reason (verified during PPS); UNK: Unknown/missing, information on indication was not verified during PPS. **Diagnosis:** see site list, only for treatment intention. **Reason in notes:** Yes - if antibiotic treatment is motivated from clinical or microbiological perspective. Otherwise - No

	HAI 1		HAI 2		HAI 3	
Case definition code						
Relevant device in situ before HAI onset (3)	O Yes O No O Unknown		O Yes O No O Unknown		O Yes O No O Unknown	
Date of onset of HAI (4)	___/___/_____		___/___/_____		___/___/_____	
Origin of infection	O current hospital O other hospital O other/unknown		O current hospital O other hospital O other/unknown		O current hospital O other hospital O other/unknown	
If BSI: source (5)						
	MO code	**R**(6)	**MO code**	**R**(6)	**MO code**	**R**(6)
Microorganism 1						
Microorganism 2						
Microorganism 3						

(3) Relevant device use (intubation for PN, CVC/PVC for BSI, urinary catheter for UTI) within 48 hours before onset of infection (even intermittent use), seven days for UTI. **(4)** Not to be recorded if signs/symptoms are present at admission, but mandatory if onset during current hospitalisation. Record the date of first signs or symptoms of the infection; if unknown, record the date treatment was started for this infection or the date the first diagnostic sample was taken. If no treatment or sample, please estimate (dd/mm/yyyy).
(5) C-CVC, C-PVC, S-PUL, S-UTI, S-DIG, S-SSI, S-SST, S-OTH, UO, UNK. **(6)** AMR marker 0, 1, 2 or 9, see table.

B – 2: Clinical Research Form for VAP Study

1. Assessment Schedule

Summary of Data Collection	Baseline	D 0	D 3	D 7	D14	Completion	Discharge	28-day follow-up
Informed consent form	M	O						
Daily assessment	Daily, until a defined endpoint is met.							
Clinical assessment (CRF)	M	M	M	M	M	M		
Antibiotic use	M					M		
Assessment of pneumonia/VAP	M							
APACHE	M							
SOFA	M	M	M	M	M			
Cost of treatment							M	
Photograph chest x-rays	M*						M	
28-day follow-up								M
Non-microbiology investigations								
Arterial blood gas (3ml blood)	M	M	M	M	M			
Complete blood count, CRP (5 ml blood)	M	M	M	M	M			
Creatinine, Bilirubin (6 ml blood)	M	M	M	M	M			
Urea, Na, K, Glucose, Albumin, LDH	M							
Chest x ray	M*	M	O	M	M			
Microbiology investigations (request susceptibility testing on all positive cultures)								
Blood culture		M					Update additional culture results	
Tracheal aspirate or sputum for culture	M	M		M				
Bronchoscopy for culture		O						

M – Mandatory; O – Optional; M* Mandatory repeat CXR after 48hrs if initial CXR abnormal lung fields.

Mandatory investigations on day of assessment: arterial blood gas, complete blood count and differential, CRP, Creatinine, total bilirubin, Urea, Na, K, Glucose, Albumin, LDH, chest x-ray

2. Baseline Assessment form

Participant number: 07RS-[__|__]-[__|__|__]

INCLUSION Criteria (all answers must be YES)				
1. Aged ≥ 18 years	O	Yes	O	No
2. Intubation or tracheostomy present	O	Yes	O	No
3. Date of intubation/trache clearly documented	O	Yes	O	No
4. Admission to ICU within the last 48 hours	O	Yes	O	No
EXCLUSION criteria (Answer must be NO)				
Evidence / suspicion of Ventilator Associated Pneumonia	O	Yes	O	No
CONSENT (Answer must be YES)				
Patient/representative has given consent	O	Yes	O	No

TIME POINTS	**DATE** *(dd/mm/yy)*	**TIME** *(24hr clock)*
1. Admission to this hospital	[__|__]/[__|__]/[__|__]	[__|__]:[__|__]
2. Date and time of intubation	[__|__]/[__|__]/[__|__]	[__|__]:[__|__]
3. Baseline assessment by study staff	[__|__]/[__|__]/[__|__]	[__|__]:[__|__]
Study staff (family name, given name)		

GENERAL INFORMATION		
1. Sex:		O Male O Female
2. Date of birth *(dd/mm/yyyy)*: If not available, record age:		[__|__]/[__|__]/[__|__|__|__] [__|__] years
3. Patient's family name, given name*:		[_____]
4. Patient's telephone*:		[_____]
5. Next of kin*	Name:	[_____]
	Telephone:	[_____]
	Relationship to patient:	[_____]
6. Hospital number:		[_____]
a. Ward: _____		O ICU NHTD O ICU Bach Mai O ICU HTD O Other
7. Health Insurance:		O Yes O No
8. Weight if scale available (kg): [__|__]	9. Height (cm): [__|__|__]	

** Information will not be entered in the database*

MEDICAL HISTORY	
1. Myocardial infarction	O Yes O No O Don't know
2. Congestive heart failure	O Yes O No O Don't know
a. NYHA class IV?	O Yes O No O Don't know
3. Peripheral vascular disease	O Yes O No O Don't know
4. Cerebrovascular disease	O Yes O No O Don't know
5. Hemiplegia	O Yes O No O Don't know
6. Dementia	O Yes O No O Don't know
7. Chronic pulmonary disease: restrictive, obstructive, or vascular	O Yes O No O Don't know
a. ANY of severe exercise restriction; documented hypoxemia or hypercapnia; secondary polycythemia; severe pulmonary hypertension (>40 mmHg); ventilator dependence	O Yes O No O Don't know
8. Connective tissue disease	O Yes O No O Don't know
9. Peptic ulcer disease	O Yes O No O Don't know
10. Mild liver disease: Chronic hepatitis or cirrhosis without portal hypertension	O Yes O No O Don't know
11. Severe liver disease: Cirrhosis with portal hypertension	O Yes O No O Don't know
12. Biopsy proven cirrhosis and documented portal hypertension; past upper GI bleeding attributed to portal hypertension; prior hepatic failure; OR prior hepatic encephalopathy	O Yes O No O Don't know
13. Chronic renal disease: Usual creatinine >175µmol/L	O Yes O No O Don't know
a. *chronic dialysis?*	O Yes O No O Don't know
14. Diabetes with no end-organ damage	O Yes O No O Don't know

MEDICAL HISTORY	
15. Diabetes with end-organ damage: *Nephropathy, retinopathy, or neuropathy*	O Yes O No O Don't know
16. Solid tumour without metastases: diagnosed in the last 5 yrs *Excluding non-melanoma skin cancer*	O Yes O No O Don't know
17. Leukemia or lymphoma	O Yes O No O Don't know
18. Metastatic cancer	O Yes O No O Don't know
19. Alcohol addiction	O Yes O No O Don't know
20. AIDS	O Yes O No O Don't know
21. Immunosuppression: chemotherapy, radiation therapy, long-term or recent high-dose steroids	O Yes O No O Don't know

DIAGNOSIS: Use ICD9	
1. ICU admission diagnosis:	[_____]
2. Status post-surgery?	O No O Elective O Emergent
3. Other diagnoses	1.
	2.
	3.

RECENT ADMISSIONS
4. Admission to any hospital for **another** illness in the last 90 days: O Yes O No O Don't know
5. Admission to another hospital for **this** illness before this hospital: O Yes O No O Don't know
a. If yes, hospital type: O Tertiary O Provincial O District
b. Date of admission to that hospital: [__|__]/[__|__]/[__|__]*(dd/mm/yy)*

ANTIMICROBIAL USE		
6. Antimicrobial use for **another** illness in the last 90 days: O Yes O No O Don't know		
7. Antimicrobial use for **this** illness (home/ referral hospital): O Yes O No O Don't know		
Generic name (or 'unknown')	**Start date *(dd/mm/yy)***	**End date *(dd/mm/yy)***
1.	[__|__]/[__|__]/[__|__]	[__|__]/[__|__]/[__|__]
2.	[__|__]/[__|__]/[__|__]	[__|__]/[__|__]/[__|__]
3.	[__|__]/[__|__]/[__|__]	[__|__]/[__|__]/[__|__]
4.	[__|__]/[__|__]/[__|__]	[__|__]/[__|__]/[__|__]
5.	[__|__]/[__|__]/[__|__]	[__|__]/[__|__]/[__|__]

INDICATION FOR INTUBATION (Check all that apply)	
8. Unable to maintain or protect airway (e.g. decreased level of consciousness, airway obstruction)	☐
9. Ventilation problem (e.g. high pCO2, depressed respiratory rate, weak respiratory muscles)	☐
10. Oxygenation problem (low paO2)	☐
11. Other reason, please describe.	☐

GCS	Before intubation	Most recent value taken on day of assessment	
12. Eyes	[__]/ 4	[__]/ 4	4 spontaneously open, 3 open to voice, 2 open to pain, 1 nil
13. Verbal	[__]/ 5	[__]/ 5	5 oriented, 4 confused, 3 random words, 2 sounds, 1 nil; '**T' if intubated**
14. Motor	[__]/ 6	[__]/ 6	6 obey commands, 5 localize pain, 4 withdraw to pain, 3 flexion, 2 extension, 1 nil

PHYSIOLOGICAL ASSESSMENT (most recent value taken on day of assessment)				
1. Temperature	[__|__].[__]°C			
	O Oral	O Tympanic	O Axillary	O Rectal
2. Heart Rate [__|__|__] bpm	3. Blood Pressure [__|__|__]/[__|__|__] mmHg			
4. Actual mean arterial pressure, if available	[__|__|__] mmHg			
5. Vasopressors (highest dose, mcg/kg/min)				
a. dobutamine	O No	O Yes		
b. dopamine	O No	O ≤ 5	O > 5	O > 15
c. noradrenaline	O No	O ≤ 0.1	O > 0.1	O >0.25
d. adrenaline	O No	O ≤ 0.1	O > 0.1	O >0.25
6. Respiratory Rate	[__|__] bpm			
7. 24-hour IV fluid infused* [__|__|__|__] ml	8. 24-hour Urine Output* [__|__|__|__] ml			

***:** record the routine value from clinical chart for the 24h period to enrolment time.

ARTERIAL BLOOD GAS (most recent value taken on day of assessment)			
9.FiO2	[__|__|__] %	12.HCO_3	[__|__] mmol/L
10.pH	[__].[__|__]	13.A-a gradient	[__|__|__] mmHg
11.PaO2	[__|__|__] mmHg	14.$PaCO_2$	[__|__|__] mmHg

LABORATORY RESULTS (most recent value taken on day of assessment)			
Hematology		**Biochemistry**	
15.White cell count	[__|__].[__] 10^9/L	20. Creatinine	[__|__|__].[__] µmol/L
a. Neutrophils	[__|__].[__] %	a. Acute renal failure? O Yes O No	
b. Lymphocytes	[__|__].[__] %	21. Urea	[__|__].[__] mmol/L
16.Hematocrit	[__|__].[__]%	22. Na+	[__|__|__] mmol/L
17.Hemoglobin	[__|__|__] g/L	23. K+	[__|__].[__] mmol/L
18.Red blood cell	[__].[__|__] 10^{12}/L	24. Glucose	[__|__].[__] mmol/L
19.Platelet count	[__|__|__] 10^9/L	25. Total bilirubin	[__|__|__] mg/L
		26. Albumin	[__|__].[__] g/L
		27. LDH	[__|__|__|__] U/L
		28. CRP	[__|__|__] µmol/L

CHEST X-RAY (most recent film taken on day of assessment)

1. Circle any infiltrates on diagram to the right.

2. Consolidation: ○ Yes ○ No

3. Cavitation: ○ Yes ○ No

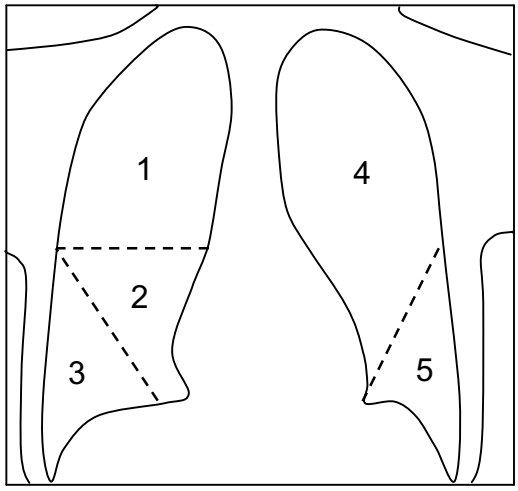
4. **CXR photograph taken:** ○ Yes

5. CXR reader 1 (family name, given name):

_____

6. CXR reader 2 (family name, given name):

_____



Next step: Proceed to **CRF daily assessment.**

3. Daily Assessment form

Participant number: 07RS-[__|__]-[__|__|__]

Date *(dd/mm/yy)*	__/__/___	__/__/___	__/__/___	__/__/___	__/__/___	__/__/___	__/__/___
1. Location *ICU/ward*	ICU / ward	ICU / ward	ICU / ward	ICU / ward	ICU / ward	ICU / ward	ICU / ward
2. Intubated? *Yes/No/T* (tracheostomy)	Yes / No / T	Yes / No / T	Yes / No / T	Yes / No / T	Yes / No / T	Yes / No / T	Yes / No / T
3. Ventilated? *Yes/No*	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No
4. None/Sedation/Paralysis/Both	No/ S / P / B	No/ S / P / B	No/ S / P / B	No/ S / P / B	No/ S / P / B	No/ S / P / B	No/ S / P / B
Systemic Criteria							
5. Max. temperature (^oC)	[__|__].[__]	[__|__].[__]	[__|__].[__]	[__|__].[__]	[__|__].[__]	[__|__].[__]	[__|__].[__]
6. Max. WBC or n/a							
7. Min. WBC							
Ventilation & secretions							
8. Min. PEEP (mmH_2O) or n/a							
9. Min. FiO_2 (%) or n/a							
10. Increase in purulent secretions? *Yes/No*	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No
11. Gram stain neutrophils ≥25/lpf *Yes/No/ na*	Yes / No / na	Yes / No / na	Yes / No / na	Yes / No / na	Yes / No / na	Yes / No / na	Yes / No / na
12. Tracheal aspirate *(TA)/* Sputum *(S)/* Bronchoscopy *(B)*	TA / S / B	TA / S / B	TA / S / B	TA / S / B	TA / S / B	TA / S / B	TA / S / B
13. Suspect VAP? *Yes/No*	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No
Antibiotic Use							
On antibiotics	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No
If yes, give indication code							
If yes give antibiotic code							
Initials of study doctor							

"NO VAP" endpoint if: Patient well 48h after extubation OR Transferred to another hospital, death while intubated, or discharged home.

→ Go to CRF Completion

Suspect VAP if :
Deterioration in ventilation AND systemic signs AND secretions

Go to 'CRF CXR' to see if VAP is confirmed.

CODES

"Deterioration in ventilation" at least one of

PEEP criteria: ≥ 2 days of stable or decreasing daily minimum **PEEP** followed by a **rise in daily minimum PEEP of ≥ 2.5 cm H_2O, sustained for ≥ 2 calendar days**;
or
FiO2 Criteria: ≥ 2 days of stable or decreasing daily minimum **FiO_2** followed by a **rise in daily minimum FiO_2 of ≥ 0.15 points, sustained for ≥ 2 calendar days**

"Systemic signs" at least one of
Fever >38ºC or <36ºC
or
WBC >12x109/L or <4x10^9/L

"Secretions" at least one of
Increased/new purulent secretions
or
>25 neutrophils per low power (x10) field on Gram stain of ET aspirate

Indication Codes

CNS	infection of central nervous system	PNEU	Pneumonia
BAC	Laboratory confirmed bacteraemia	BRON	Acute bronchitis, trachea-bronchitis, excacerbation of chronic bronchitis
CSEP	Clinical sepsis	EYE	Endopthalmitis
ENT	Infection of ear, nose, throat	CVS	Endocarditis, vascular graft infection
IA	Intra-abdominal sepsis	GI	Gastrointestinal infection (eg salmonellosis, antibiotic associated colitis)
SST	Skin or soft tissue infection	BJ	Bone or joint infection
CYS	Lower urinary tract (eg cystitis)	PYE	Upper urinary tract (pyelonephritis)
ASB	Asymptomatic bacteruria	OBGY	Obstetric/gynaecological infection/STI in women
GUM	STI in men, prostatitis, epididymo-orchitis etc	SIRS	systemic inflammatory response wityh no clear anatomical site
FN	Febrile neutropenia	UND	site with no systemic inflammation

Antibiotic codes (can put more than one)

1 Colistin	2 Carbapenem	3 Aminoglycoside	4 Fourth gen cephalosporin *or* βlactam+ βlactamase inhibitor	5 Other

4. Chest X-Ray Assessment form

Participant number: 07RS-[__|__]-[__|__|__]

Date of assessment: [__|__]/[__|__]/[__|__] *(dd/mm/yy)*

Time of assessment: [__|__]:[__|__] *(hh:mm – 24hr clock)*

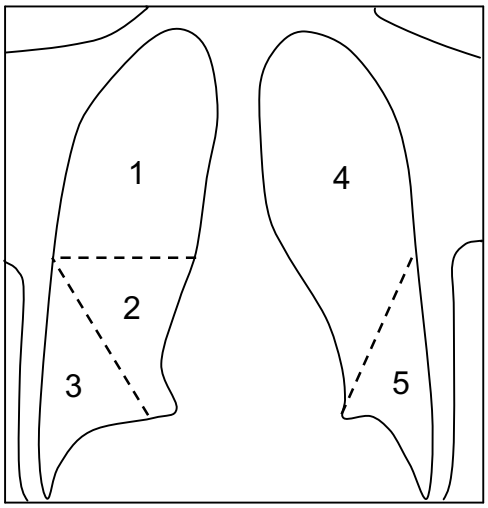
CHEST X-RAY

1. Date of last chest x-ray for comparison:

   [__|__]/[__|__]/[__|__] *(dd/mm/yy)*

2. Is there a new infiltrate on this chest x-ray?

   ○ Yes ○ No ○ Not done



3. Circle all infiltrates on diagram to the right.
4. Consolidation: ○ Yes ○ No
5. Cavitation: ○ Yes ○ No
6. **CXR photograph taken:** ○ Yes
7. CXR reader 1 (family name, given name): _____
8. CXR reader 2 (family name, given name): _____

Q2 Outcome – Was there new infiltrates on the CXR?
Yes: VAP, go to 'CRF VAP case'.
No or not done: Go to question 9

9. Has a new antibiotic been started for a respiratory tract infection within the last 48 hrs:
   Yes: VAP, go to 'CRF VAP case'.
   No: continue with "Daily assessment CRF"

5. Additional Microbiology Assessment form

CRF Additional Microbiology	**MICRO**
Participant number: 07RS-[__|__]-[__|__|__]	Page __ of __

1. Blood Culture

a. Laboratory specimen number: [_____]
b. Date taken: [__|__]/[__|__]/[__|__] *(dd/mm/yy)*
c. Any antibiotics received before specimen taken? O Yes O No
d. Culture report (attach copy of susceptibility test)
[_____]
OR, Negative culture after 5 days ☐

2. Respiratory culture

a. Collection: O Bronchoscopy O Tracheal Aspirate O Sputum
b. Sputum: adequate specimen? (≥25 polymorphs and ≤10 squamous cells): O Yes O No
c. Tracheal aspirate: ≥25 polymorphs? O Yes O No
d. Laboratory specimen number: [_____]
e. Date taken: [__|__]/[__|__]/[__|__] *(dd/mm/yy)*
f. Any antibiotics received before specimen taken? O Yes O No
g. Gram stain morphology: [_____]
h. Culture report (bacteria and amount of growth e.g. 1+/2+; attach copy of susceptibility test)
[_____]
OR, Negative culture ☐

CRF Additional Microbiology	**MICRO**
Participant number: 07RS-[__|__]-[__|__|__]	Page __ of __

1. Blood Culture

a. Laboratory specimen number: [_____]
b. Date taken: [__|__]/[__|__]/[__|__] *(dd/mm/yy)*
c. Any antibiotics received before specimen taken? O Yes O No
d. Culture report (attach copy of susceptibility test)
[_____]
OR, Negative culture after 5 days ☐

2. Respiratory culture

a. Collection: O Bronchoscopy O Tracheal Aspirate O Sputum
b. Sputum: adequate specimen? (≥25 polymorphs and ≤10 squamous cells): O Yes O No
c. Tracheal aspirate: ≥25 polymorphs? O Yes O No
d. Laboratory specimen number: [_____]
e. Date taken: [__|__]/[__|__]/[__|__] *(dd/mm/yy)*
f. Any antibiotics received before specimen taken? O Yes O No
g. Gram stain morphology: [_____]
h. Culture report (bacteria and amount of growth e.g. 1+/2+; attach copy of susceptibility test)
[_____]
OR, Negative culture ☐

6. VAP Assessment form

DAY OF VAP DIAGNOSIS (DAY 0)

1. Participant number: 07RS-[__|__]-[__|__|__]
2. Date of assessment: [__|__]/[__|__]/[__|__] *(dd/mm/yy)*
3. Time of assessment: [__|__]:[__|__] *(hh:mm – 24hr clock)*
4. Study staff (family name, given name):
   [_____]

Mandatory investigations on VAP day 0: arterial blood gas, complete blood count and differential, CRP, Creatinine, total bilirubin, chest x-ray, blood culture and susceptibility, tracheal aspirate/sputum for culture and susceptibility
Optional investigations: bronchoscopy for bronchoalveolar lavage → culture and susceptibility

5. **GCS**		**(most recent value taken on VAP day 0)**
a. Eyes	[__]/ 4	4 spontaneously open, 3 open to voice, 2 open to pain, 1 nil
b. Verbal	[__]/ 5	5 oriented, 4 confused, 3 random words, 2 sounds, 1 nil; **write 'T' if intubated**
c. Motor	[__]/ 6	6 obey commands, 5 localize pain, 4 withdraw to pain, 3 flexion, 2 extension, 1 nil

PHYSIOLOGICAL ASSESSMENT (most recent value taken on VAP day 0)				
6. Temperature [__|__].[__]°C O Oral O Tympanic O Axillary O Rectal				
7. Heart Rate [__|__|__] bpm	8. Blood Pressure [__|__|__]/[__|__|__] mmHg			
9. Actual mean arterial pressure, if available	[__|__|__] mmHg			
10. Vasopressors (highest dose, mcg/kg/min)				
e. Dobutamine	O No	O Yes		
f. Dopamine	O No	O ≤ 5	O > 5	O > 15
g. Noradrenaline	O No	O ≤ 0.1	O > 0.1	O >0.25
h. adrenaline	O No	O ≤ 0.1	O > 0.1	O >0.25
11. Respiratory Rate	[__|__] bpm			
12. 24-hour IV fluid infused* [__|__|__|__] ml	13. 24-hour Urine Output* [__|__|__|__] ml			

***:** record the routine value from clinical chart for the 24h period which covers VAP day 0.

LABORATORY RESULTS (most recent value taken on VAP day 0)			
Hematology		**Biochemistry**	
14. White cell count	[__|__].[__] 10^9/L	18. Creatinine	[__|__|__].[__] µmol/L
a. Neutrophils	[__|__].[__] %	19. Total bilirubin	[__|__|__] mg/L
b. Lymphocytes	[__|__].[__] %	20. CRP	[__|__|__] µmol/L
15. Hematocrit	[__|__].[__]%		
16. Hemoglobin	[__|__|__] g/L	**Arterial blood gas**	
17. Red blood cell	[__].[__|__] 10^{12}/L	21. PaO_2	[__|__|__] mmHg
18. Platelet count	[__|__|__] 10^9/L	22. FiO_2	[__|__|__] %

23. Blood Culture

e. Laboratory specimen number: [_____]

f. Date taken: [__|__]/[__|__]/[__|__] *(dd/mm/yy)*

g. Any antibiotics received before specimen taken? O Yes O No

h. Culture report (attach copy of susceptibility test)

[_____]

OR, Negative culture after 5 days ☐

24. Respiratory culture

i. Collection: O Bronchoscopy O Tracheal Aspirate O Sputum

j. Sputum: adequate specimen? (≥25 polymorphs and ≤10 squamous cells): O Yes O No

k. Tracheal aspirate: ≥25 polymorphs? O Yes O No

l. Laboratory specimen number: [_____]

m. Date taken: [__|__]/[__|__]/[__|__] *(dd/mm/yy)*

n. Any antibiotics received before specimen taken? O Yes O No

o. Gram stain morphology: [_____]

p. Culture (bacteria and amount of growth e.g. 1+/2+; attach copy of susceptibility test)

[_____]

OR, Negative culture ☐

25. Respiratory culture

a. Collection: O Bronchoscopy O Tracheal Aspirate O Sputum

b. Sputum: adequate specimen? (≥25 polymorphs and ≤10 squamous cells): O Yes O No

c. Tracheal aspirate: ≥25 polymorphs? O Yes O No

d. Laboratory specimen number: [_____]

e. Date taken: [__|__]/[__|__]/[__|__] *(dd/mm/yy)*

f. Any antibiotics received before specimen taken? O Yes O No

g. Gram stain morphology: [_____]

h. Culture (bacteria and amount of growth e.g. 1+/2+; attach copy of susceptibility test)

[_____]

OR, Negative culture ☐.

DAY 3 AFTER VAP DIAGNOSIS

1. Participant number: 07RS-[__|__]-[__|__|__]
2. Date of assessment: [__|__]/[__|__]/[__|__] *(dd/mm/yy)*
3. Time of assessment: [__|__]:[__|__] *(hh:mm – 24hr clock)*
4. Study staff (family name, given name):
   [_____]

Update culture results from VAP day 0: ☐ Yes

Mandatory investigations on VAP day 3: arterial blood gas, complete blood count and differential, CRP, Creatinine, total bilirubin

Optional investigations: chest x-ray

5. GCS		**(most recent value taken on VAP day 3)**
a. Eyes	[__]/4	4 spontaneously open, 3 open to voice, 2 open to pain, 1 nil
b. Verbal	[__]/5	5 oriented, 4 confused, 3 random words, 2 sounds, 1 nil; write 'T' if intubated
c. Motor	[__]/6	6 obey commands, 5 localize pain, 4 withdraw to pain, 3 flexion, 2 extension, 1 nil

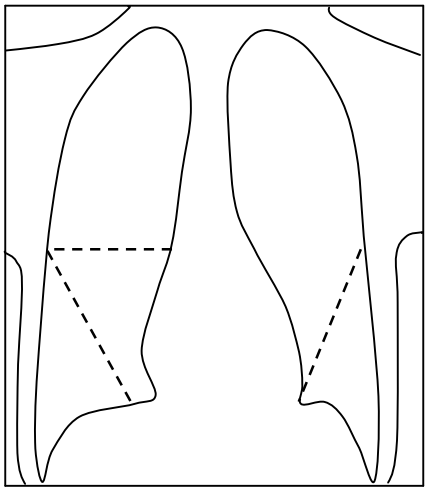
PHYSIOLOGICAL ASSESSMENT	**(most recent value taken on VAP day 3)**			
6. Temperature	[__|__].[__]°C ○ Oral ○ Tympanic ○ Axillary ○ Rectal			
7. Heart Rate [__|__|__] bpm	8. Blood Pressure [__|__|__]/[__|__|__] mmHg			
9. Actual mean arterial pressure, if available	[__|__|__] mmHg			
10. Vasopressors (highest dose, mcg/kg/min)				
a. dobutamine	○ No	○ Yes		
b. dopamine	○ No	○ ≤ 5	○ > 5	○ > 15
c. noradrenaline	○ No	○ ≤ 0.1	○ > 0.1	○ >0.25
d. adrenaline	○ No	○ ≤ 0.1	○ > 0.1	○ >0.25
11. Respiratory Rate	[__|__] bpm			
12. 24-hour IV fluid infused* [__|__|__|__] ml	13. 24-hour Urine Output* [__|__|__|__] ml			

***:** record the routine value from clinical chart for the 24h period which covers VAP day 3.

LABORATORY RESULTS (most recent value taken on VAP day 3)			
Hematology		**Biochemistry**	
14. White cell count	[__|__].[__] 10^9/L	19. Creatinine	[__|__|__].[__] µmol/L
c. Neutrophils	[__|__].[__] %	20. Total bilirubin	[__|__|__] mg/L
d. Lymphocytes	[__|__].[__] %	21. CRP	[__|__|__] µmol/L
15. Hematocrit	[__|__].[__]%		
16. Hemoglobin	[__|__|__] g/L	**Arterial blood gas**	
17. Red blood cell	[__].[__|__] 10^{12}/L	22. PaO_2	[__|__|__] mmHg
18. Platelet count	[__|__|__] 10^9/L	23. FiO_2	[__|__|__] %

CHEST X-RAY (Optional; most recent film taken on VAP day 3)

1. Date of last chest x-ray for comparison: [__|__]/[__|__]/[__|__] *(dd/mm/yy)*
2. Compared to last chest-x-ray (overall impression):
   ○ better ○ worse ○ same
3. Circle all infiltrates on diagram to the right.
4. Consolidation: ○ Yes ○ No
5. Cavitation: ○ Yes ○ No
6. **CXR photograph taken:** ○ Yes
7. CXR reader 1 (family name, given name): _____
8. CXR reader 2 (family name, given name): _____



DAY 7 AFTER VAP DIAGNOSIS

1. Participant number: 07RS-[__|__]-[__|__|__]
2. Date of assessment: [__|__]/[__|__]/[__|__] *(dd/mm/yy)*
3. Time of assessment: [__|__]:[__|__] *(hh:mm – 24hr clock)*
4. Study staff (family name, given name):
   [_____]

Update culture results from VAP day 3: ☐ Yes

Mandatory investigations on VAP day 7: arterial blood gas, complete blood count and differential, CRP, Creatinine, total bilirubin, chest x-ray

5. GCS	**(most recent value taken on VAP day 7)**
a. Eyes [__]/ 4	4 spontaneously open, 3 open to voice, 2 open to pain, 1 nil
b. Verbal [__]/ 5	5 oriented, 4 confused, 3 random words, 2 sounds, 1 nil; **write 'T' if intubated**
c. Motor [__]/ 6	6 obey commands, 5 localize pain, 4 withdraw to pain, 3 flexion, 2 extension, 1 nil

PHYSIOLOGICAL ASSESSMENT (most recent value taken on VAP day 7)				
6. Temperature [__|__].[__]°C O Oral O Tympanic O Axillary O Rectal				
7. Heart Rate [__|__|__] bpm	8. Blood Pressure [__|__|__]/[__|__|__] mmHg			
9. Actual mean arterial pressure, if available	[__|__|__] mmHg			
10. Vasopressors (highest dose, mcg/kg/min)				
a. dobutamine	O No	O Yes		
b. dopamine	O No	O ≤ 5	O > 5	O > 15
c. noradrenaline	O No	O ≤ 0.1	O > 0.1	O >0.25
d. adrenaline	O No	O ≤ 0.1	O > 0.1	O >0.25
11. Respiratory Rate	[__|__] bpm			
12. 24-hour IV fluid infused* [__|__|__|__] ml	13. 24-hour Urine Output* [__|__|__|__] ml			

***:** record the routine value from clinical chart for the 24h period which covers VAP day 7.

LABORATORY RESULTS (most recent value taken on VAP day 7)			
Hematology		**Biochemistry**	
14. White cell count	[__|__].[__] 10^9/L	19. Creatinine	[__|__|__].[__] µmol/L
a. Neutrophils	[__|__].[__] %	20. Total bilirubin	[__|__|__] mg/L
b. Lymphocytes	[__|__].[__] %	21. CRP	[__|__|__] µmol/L
15. Hematocrit	[__|__].[__]%		
16. Hemoglobin	[__|__|__] g/L	**Arterial blood gas**	
17. Red blood cell	[__].[__|__] 10^{12}/L	22. PaO_2	[__|__|__] mmHg
18. Platelet count	[__|__|__] 10^9/L	23. FiO_2	[__|__|__] %

CHEST X-RAY (most recent film taken on VAP day 7)

7. Date of last chest x-ray for comparison: [__|__]/[__|__]/[__|__] *(dd/mm/yy)*

8. Compared to last chest-x-ray (overall impression):
O better O worse O same

9. Circle all infiltrates on diagram to the right.

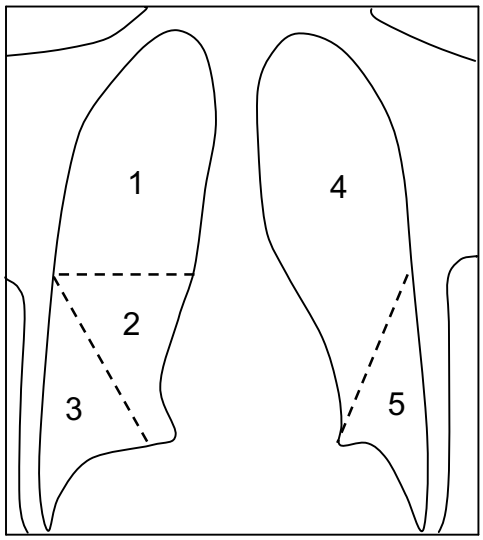
10. Consolidation: O Yes O No

11. Cavitation: O Yes O No

12. **CXR photograph taken:** O Yes

13. CXR reader 1 (family name, given name):
_____

14. CXR reader 2 (family name, given name):
_____



DAY 14 AFTER VAP DIAGNOSIS

1. Participant number: 07RS-[__|__]-[__|__|__]
2. Date of assessment: [__|__]/[__|__]/[__|__] *(dd/mm/yy)*
3. Time of assessment: [__|__]:[__|__] *(hh:mm – 24hr clock)*
4. Study staff (family name, given name):

Update antibiotics and culture results from VAP day 7: ☐ Yes

Mandatory investigations on VAP day 14: arterial blood gas, complete blood count and differential, CRP, Creatinine, total bilirubin, chest x-ray

5. **GCS**	**(most recent value taken on VAP day 14)**
a. Eyes [__]/ 4	4 spontaneously open, 3 open to voice, 2 open to pain, 1 nil
b. Verbal [__]/ 5	5 oriented, 4 confused, 3 random words, 2 sounds, 1 nil; write 'T' if intubated
c. Motor [__]/ 6	6 obey commands, 5 localize pain, 4 withdraw to pain, 3 flexion, 2 extension, 1 nil

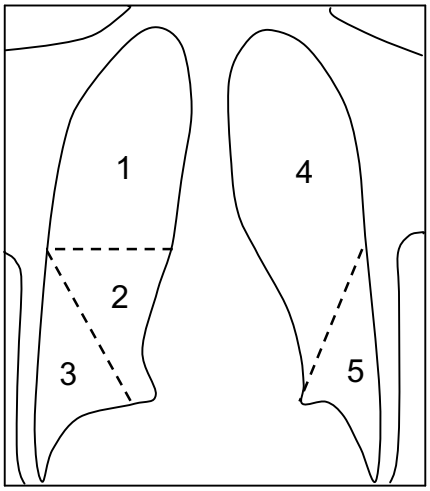
PHYSIOLOGICAL ASSESSMENT (most recent value taken on VAP day 14)				
6. Temperature [__|__].[__]°C O Oral O Tympanic O Axillary O Rectal				
7. Heart Rate [__|__|__] bpm	8. Blood Pressure [__|__|__]/[__|__|__] mmHg			
9. Actual mean arterial pressure, if available	[__|__|__] mmHg			
10. Vasopressors (highest dose, mcg/kg/min)				
a. dobutamine	O No	O Yes		
b. dopamine	O No	O ≤ 5	O > 5	O > 15
c. noradrenaline	O No	O ≤ 0.1	O > 0.1	O >0.25
d. adrenaline	O No	O ≤ 0.1	O > 0.1	O >0.25
11. Respiratory Rate	[__|__] bpm			
12. 24-hour IV fluid infused* [__|__|__|__] ml	13. 24-hour Urine Output* [__|__|__|__] ml			

*: record the routine value from clinical chart for the 24h period which covers VAP day 14.

LABORATORY RESULTS (most recent value taken on VAP day 14)			
Hematology		**Biochemistry**	
14. White cell count	[__|__].[__] 10^9/L	19. Creatinine	[__|__|__].[__] µmol/L
a. Neutrophils	[__|__].[__] %	20. Total bilirubin	[__|__|__] mg/L
a. Lymphocytes	[__|__].[__] %	21. CRP	[__|__|__] µmol/L
15. Hematocrit	[__|__].[__]%		
16. Hemoglobin	[__|__|__] g/L	**Arterial blood gas**	
17. Red blood cell	[__].[__|__] 10^{12}/L	22. PaO_2	[__|__|__] mmHg
18. Platelet count	[__|__|__] 10^9/L	23. FiO_2	[__|__|__] %

CHEST X-RAY (most recent film taken on VAP day 14)

1. Date of last chest x-ray for comparison:
   [__|__]/[__|__]/[__|__] *(dd/mm/yy)*
2. Compared to last chest-x-ray (overall impression):
   a. ○ better ○ worse ○ same
3. Circle all infiltrates on diagram to the right.
4. Consolidation: ○ Yes ○ No
5. Cavitation: ○ Yes ○ No
6. **CXR photograph taken:** ○ Yes
7. CXR reader 1 (family name, given name):
   _____
8. CXR reader 2 (family name, given name):
   _____



Next step: go to **CRF completion**

7. Complete Assessment form

1. Participant number: 07RS-[__|__]-[__|__|__]
2. Date of assessment: [__|__]/[__|__]/[__|__] *(dd/mm/yy)*
3. Time of assessment: [__|__]:[__|__] *(hh:mm – 24hr clock)*
4. Study staff (family name, given name): [_____]

STUDYCOMPLETION choose **one only**		Date *(dd/mm/yy)*
5. **VAP:** Day 28 after VAP diagnosis	• Patient remains in hospital	[__|__]/[__|__]/[__|__]
	• Discharged already	[__|__]/[__|__]/[__|__]
6. **No VAP:** Day 28 after enrolment	• Patient well 48h after extubation or still intubated	[__|__]/[__|__]/[__|__]
	• Discharged already	[__|__]/[__|__]/[__|__]

DISCHARGE DETAILS			
7. Discharge Date		[__|__]/[__|__]/[__|__]	
DISCHARGE REASON (choose only one)			
8. Discharged home, stable	O Yes	9. Transferred to another hospital	O Yes
10. Discharged home to die	O Yes	11. Death in hospital, respiratory cause	O Yes
12. Death in hospital, non-respiratory cause or unclear cause			O Yes

13. **Diagnoses: <u>final admission diagnosis</u> and any <u>additional diagnoses</u> after admission:** refer to baseline assessment; (e.g. meningitis, endocarditis)
i.
ii.
iii.
14. **Additional positive cultures from blood, sputum, or tracheal aspirate?** O Yes O No
• If yes, please complete "additional cultures" form • Attach copies of all susceptibility testing to the CRF ☐ Yes
15. **Chest x-rays: photograph and save all chest x-rays** ☐ Yes

16. **GCS** **(most recent value taken on day of completion)**	
a. Eyes [__]/ 4	4 spontaneously open, 3 open to voice, 2 open to pain, 1 nil
b. Verbal [__]/ 5	5 oriented, 4 confused, 3 random words, 2 sounds, 1 nil; <u>write 'T' if intubated</u>
c. Motor [__]/ 6	6 obey commands, 5 localize pain, 4 withdraw to pain, 3 flexion, 2 extension, 1 nil

INTUBATION enter all dates as*(dd/mm/yy)*			**VENTILATION**		**ICU stay**	
Start date	Stop date	Extubation intentional?	Start date	Stop date	Start date	Stop date
		O Yes O No				
		O Yes O No				
		O Yes O No				

ANTIBIOTICS USED in this hospital, until study outcome reached						
Brand or generic name§	Indication*	Amount per dose	Doses per day	Start date *(dd/mm/yy)*	End date *(dd/mm/yy)*	Treatment ongoing?
						O Yes
						O Yes
						O Yes
						O Yes
						O Yes
						O Yes
						O Yes
						O Yes
						O Yes

§ For tuberculosis, write "TB treatment".
*Indication: CI: community-acquired infection; LI: infection acquired at a long-term or chronic- care facility; VAP: ventilator-associated pneumonia; HI: hospital-acquired infection, not VAP; SP: surgical prophylaxis; MP: medical prophylaxis; O: other; UI: unknown indication (medical team suspect infection but source unclear); UNK: truly unknown to study doctor completing CRF

OTHER MEDICATIONS (Yes if ever used)	
17. Sedatives (e.g. benzodiazepines, anti-psychotics, anti-	O Yes O No
18. Neuromuscular blockade	O Yes O No
19. Antacids (e.g. H2-blocker or proton pump inhibitor)	O Yes O No
20. Insulin	O Yes O No
21. Steroids	O Yes O No
22. Vasopressors	O Yes O No
MEDICAL INTERVENTION (Yes if ever used)	
23. Hemodialysis	O Yes O No
24. Transfusion of blood products	O Yes O No
25. Tracheostomy a. if Yes, date of insertion [__|__]/[__|__]/[__|__] *(dd/mm/yy)*	O Yes O No
26. Thoracentesis	O Yes O No
Other, specify:	
COSTS FOR TREATMENT (attach copy of itemized costs ☐ Yes)	
27. Total cost (VND): [_____]	
28. Amount covered by health insurance: [_____]	
PHONE FOLLOW-UP AT 28 DAYS if discharged or transferred beforehand	
29. Date of assessment: [__|__]/[__|__]/[__|__] *(dd/mm/yy)*	
30. Study staff (family name, given name): [_____]	
31. Outcome	O Death O Alive, If alive: O home O another hospital O Unable to reach patient or next of kin

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